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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

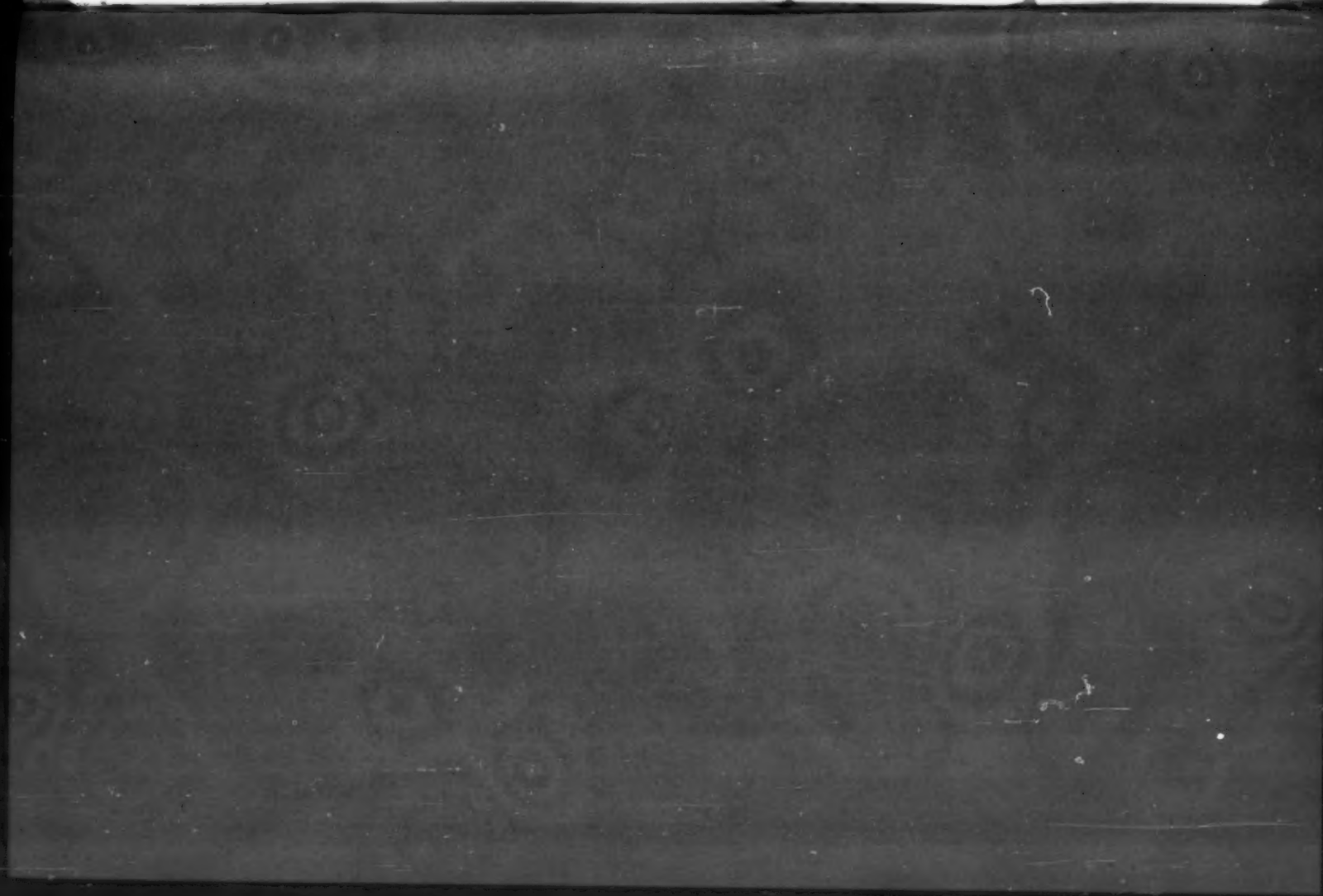
by

LEONARD A. SCHEELE

R. H. SMITHWICK

HARRY MOST

PROPOSED HOSPITAL BOND ISSUE



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BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

CONTENTS

A General View of Cancer Research 671
Leonard A. Scheele

An Evaluation of the Surgical Treatment of
Hypertension 698
R. H. Smithwick

Recent Advances in the Therapy of the More Common
Protozoan and Helminthic Infections of Man . . 717
Harry Most

The New York Academy of Medicine:
Its First Hundred Years—Philip Van Ingen . . . 741
A Review—*Mahlon Ashford*

Report of Subcommittee on
Proposed Hospital Bond Issue 743

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

NOVEMBER 1949

A GENERAL VIEW OF CANCER RESEARCH*

The Fourth James Ewing Memorial Lecture

LEONARD A. SCHEELE

Surgeon General, U. S. Public Health Service, Federal Security Agency

SOME years have passed since cancer patients and the medical profession last benefited by direct association with Dr. James Ewing. Yet those who knew him (and there are many of us present who did) surely retain a vivid impression of his personality and genius, which seem to transcend time. My words could add nothing to your experience. Those who did not have the fortune of his acquaintance may know him as a legend—as one who devoted the major part of his life to the study and diagnosis of cancer; as scholar, author, teacher; and as one of the scientific founders of Memorial Hospital. Such a conception is a true one. But legendary figures, as they grow in repute, may dwindle in humanity—become less real. So rather than discuss his work, I should like only to say, of the man himself, that James Ewing was intensely human—incisive, sincere, altruistic—one who sought truths, and found them, in the study of human nature as well as disease. No lines in epitaph could be more fitting than those of Lowell:

Great truths are portions of the soul of man;
Great souls are portions of eternity.

* Delivered at the Stated Meeting of The New York Academy of Medicine, May 5, 1949.

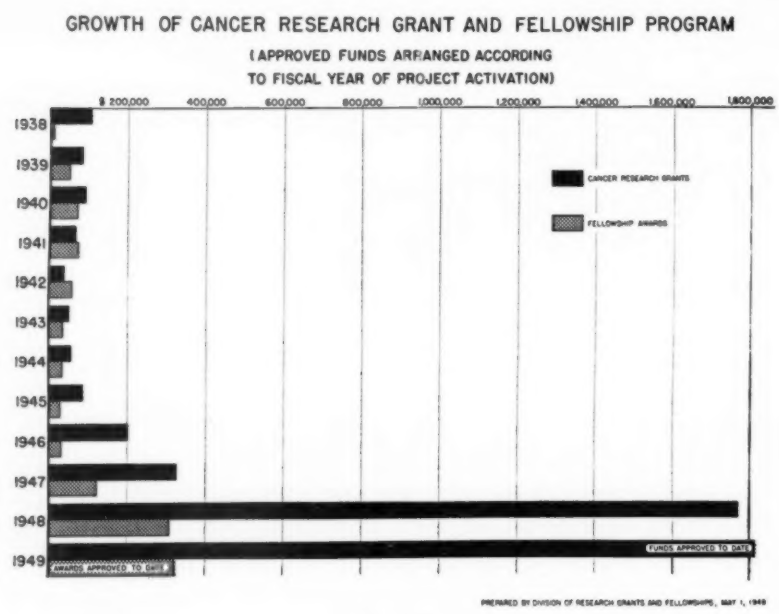


Chart 1

To have been asked to speak tonight before this group, assembled in memory of Dr. Ewing, is indeed an honor.

Dr. L'Esperance, in her cordial invitation, suggested the theme of cancer research and the Public Health Service program in this field. The subject seems particularly appropriate in view of the growth of cancer research in recent years, largely as a result of the mounting interest of the American public and medical profession, the rising hope that research will ultimately defeat this disease, and the augmented role of the American Cancer Society and the Federal Government in the national cancer research movement.

I should like, first, to describe briefly the Federal cancer research program. In the early 1920's two groups of United States Public Health Service scientists—one in Washington, D. C., the other on the campus of Harvard University—initiated projects in this field. Under the National Cancer Act of 1937, these groups were merged to form the nucleus of the National Cancer Institute. This is one of the National

GEOGRAPHIC DISTRIBUTION OF
NATIONAL CANCER INSTITUTE RESEARCH GRANT FUNDS
IN PROPORTION TO REQUESTS

1937 THROUGH APRIL 30, 1949

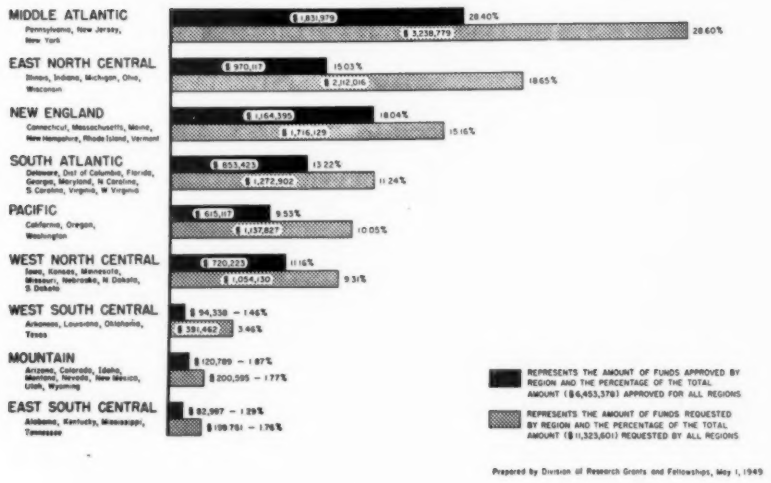


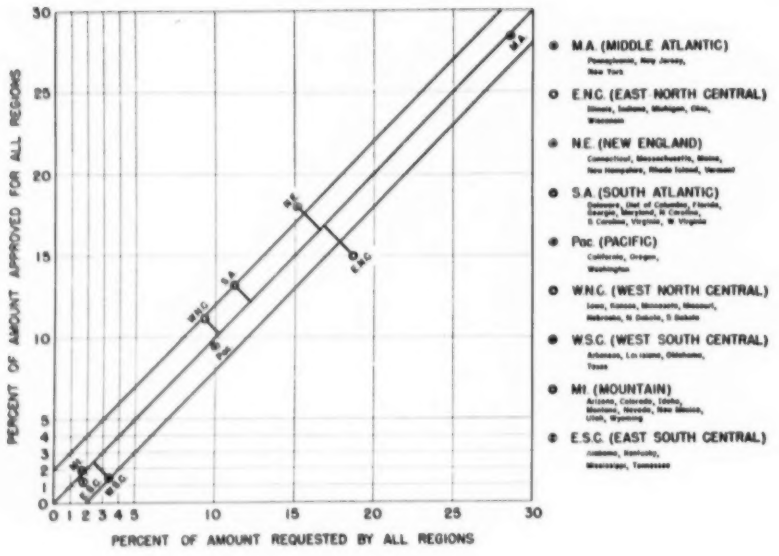
Chart 2

Institutes of Health, the principal research branch of the Public Health Service. As many of you know, the research of the Cancer Institute is conducted, for the most part, in two well-equipped buildings, completed in 1939 and early 1948 at Bethesda, Maryland.

The research at Bethesda, however, is only a small part of that financed by the Government through the Institute. I refer now to the Federal program of grants to support cancer investigation in outside institutions, a new venture of the Public Health Service when the Institute was established. This program is conducted with the advice of a National Advisory Cancer Council, provided by the National Cancer Act. The Council is composed of six leading non-Government authorities in cancer, who serve three-year terms. It advises on Institute plans and policies, and reviews and makes recommendations on grant-in-aid applications. The Surgeon General, as Council chairman, is in turn authorized to make the grants.

NATIONAL CANCER INSTITUTE RESEARCH GRANT FUNDS
APPROVED IN RELATION TO THOSE REQUESTED BY REGION

1937 THROUGH APRIL 30, 1949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W.N.C. (WEST NORTH CENTRAL)
W.S.C. (WEST SOUTH CENTRAL)
Mt. (MOUNTAIN)
E.S.C. (EAST SOUTH CENTRAL)

Chart 3

The growth of the grant-in-aid program is represented in Chart 1. Each black bar shows the total amount granted that year for cancer research in nonfederal institutions, and the shaded bars represent the amounts awarded for research fellowships. It should be pointed out that the bars represent projects started each year, and taken singly do not necessarily reflect annual Congressional appropriations, though in the aggregate they do. Research fellowships are awarded to increase the number of scientists trained in disciplines through which the cancer problem can be attacked. On the first of May 1949, there were 100 National Cancer Institute research fellows in active training in the United States and abroad.

Chart 2 presents a geographic distribution of cancer research grants and requests since the inception of the program. Other data indicate that this material reflects, quite accurately, the distribution of all

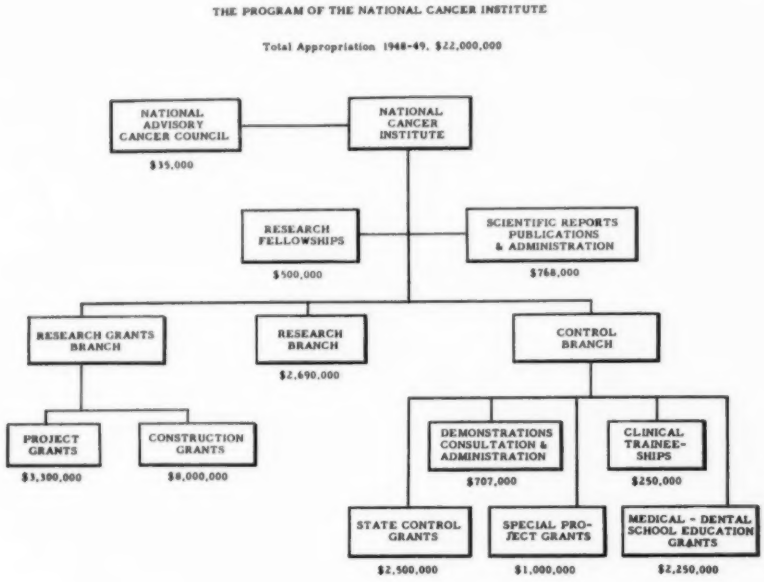

Chart 4

cancer research and 'research potential' throughout the country. For the past two years, grants for the construction of research facilities (not shown in this chart) have helped to increase the research potential of the less active areas.

The same data were used in preparing Chart 3, which presents a comparison of the amount awarded and that requested, by region. Only the applications the Council has acted on are represented: some requests have been withdrawn and a few await further investigation. The proximity of plotted points to the diagonal line reflects a nearly constant ratio of approved to requested grants.*

In 1947 the National Cancer Institute was reorganized to provide for effective integration of a much-expanded program. Chart 4 shows the allotment of appropriation for the fiscal year 1949. It shows that the activities of the Institute are administratively divided into three major fields—research grants to outside institutions, scientific research

* Deviation is greatest for the Southwest, which made only a few applications, and those for large sums.

within the Institute, and cancer control. Of the total appropriation of $22,000,000 for this year, more than half, $11,300,000, has been allocated for research grants—$8,000,000 of that, for construction of cancer research facilities. About twelve per cent of the total appropriation, $2,690,000, will be spent on intramural research; and about thirty per cent, $6,707,000, on cancer control.

If these activities were presented in detail, they would illustrate the breadth of the cancer research field—the diversity of approaches, the multiplicity of disciplines applied to fight this disease. No stronghold against science is under a more varied attack. In the remainder of my paper, I have tried to present a general view of the scientific problem posed by cancer. And now, in the hope that this view will be of interest, I should like to discuss in relatively nontechnical terms, the investigative aspects of cancer research.

Pasteur, in defining *science*, wrote that it is "built up of successive solutions given to questions of ever-increasing subtlety, approaching nearer and nearer towards the very essence of phenomena."[1] This statement seems especially applicable to cancer research. Nearly every method whereby other diseases were controlled has been tried—serologic techniques, the search for a microörganism, a decisive dietary factor, a curative drug. Some of these approaches, of course, still hold promise; but refinements inconceivable to the early workers seem necessary. We must continue to answer "questions of ever-increasing subtlety."

Consider, for instance, the matter of etiology. With the discovery, in many diseases, of a causative microörganism or its vector, the problem of control was well in hand. Other diseases were found to result from a dietary deficiency, and still others followed a simple genetic pattern. For all practical purposes, the discovery of a cause closed the question of etiology. In the study of cancer, however, investigation has disclosed a gamut of etiologic agents and influences. Let me enumerate briefly: energy agents, such as X-rays, radioactive substances, ultraviolet rays, and heat; more than 300 chemical compounds; viruses; parasites (which may be vectors for viruses); endocrine and dietary manipulations; and multiple genetic factors.[2] We are at liberty to regard cancer as one disease with a variety of possible causes, or as a number of diseases.

To know ways to produce cancer is by no means to have found 'the cause,' for most tumors are not attributable to known carcinogens.

And if subtlety is in order, it may be said that the purpose of studying cancer etiology is no longer to find the cause, but to *explain the origin.*

A large part of cancer research in this country and abroad is devoted to the study of tumor genesis and early development, since elucidation of these processes would, in all probability, lead not only to preventive measures but also to improved diagnosis and therapy. This may be the long way, but it seems sure. In discussing studies of origin and development, I shall observe a broad classification into fundamental biologic investigation and studies of carcinogenic agents and influences.

Although the term *cancer* is usually associated with a complex of phenomena, including invasion, metastasis and other aberrations of growth, the most prominent characteristic of the disease is the excessive, inexorable proliferation of cells. That characteristic is well recognized: I mention it only to illustrate that cancer is a disease of the mechanism whereby tissues are formed or replenished—the forces controlling the type of cells engendered and the direction and cessation of growth. In this light we see clearly the importance of investigating basic biologic processes, such as cell division, differentiation and adaptation.

In recent years the intracellular movements involved in mitosis have been investigated in terms of tension resulting from changes in the viscosity of protoplasm. Studies by Chalkley, Marsland and others indicate that cell division depends, to some extent, upon colloidal fluctuations between sol and gel.[3] One can hope that the fluctuations will in turn be explained. But the problem, it would seem, approaches a basic physical level, where it can be studied in terms of factors affecting colloids, such as pressure, temperature and chemical composition.

During the past decade, the intracellular microcosm has been under exploration with the electron microscope, which is about a hundred times as powerful as previous instruments. Recent studies by Porter and others have disclosed entities that may represent the underlying structure of cytoplasm.[4] In combination with ultracentrifugation, ultrafiltration and other newly developed techniques, the electron microscope may yet reveal characteristics of the cancer cell that will elucidate its origin and activity.

The processes of differentiation and regeneration are studied because of possible similarities to carcinogenesis and subsequent anaplasia. Both differentiation and carcinogenesis apparently result in a new type of cell. The former process, however, is consistent with the total pattern

of cellular organization—it is controlled; whereas in carcinogenesis, the part defies the whole. The processes may also differ in direction: that is, the cells in differentiation become, as a rule, more specialized; whereas in tumors they seem to dedifferentiate, to form tissues more like each other, morphologically and chemically, than were the tissues of origin.[5,6] It appears, however, that dedifferentiation may also occur in noncancerous development. In lower forms such as Amphibia, regeneration, as in a healing wound, is reported by Rose to involve dedifferentiation as a primary stage;[7] and in tissue culture morphologic simplification has been observed by Fischer and others in cells of even higher vertebrates.[8] Whether controlled dedifferentiation occurs, however, *in vivo* in higher animals, such as man, is still unknown.

To explain the relation of differentiation to cancer, much basic information is needed. We should like to know, for instance, whether the level of differentiation influences susceptibility of the cell to carcinogens. Clarification of the identity and role of 'organizers' would be valuable. In these and other basic biologic investigations, lower forms lend themselves well to study: the planarian, noted for its remarkable ability to regenerate a head; the hydra, whose cells after passage through a strainer will reassemble to form whole animals; the platy fish [Platypoecilus], because of its wide regenerative capacity, its response to androgen, and its susceptibility to melanoma in certain hybrids. Studies of differentiation represent attempts to relate carcinogenesis to the source of cellular variation, a process of which far too little is known.

One type of cellular variation is represented in adaptation to an unfavorable environment. Many scientists believe that all living organisms, including the cells of a multicellular species, are endowed with a capacity to adapt. This suggests a point of view from which cancer may be regarded. Carcinogenesis may be the manifestation of an attempt of cells to survive through adaptation. From the standpoint of the host, cancer certainly represents the antithesis of a tendency toward survival; but we cannot deny that a cancer cell, among its normal neighbors, is an exalted being. And one could add that its destruction of the host does not debase the concept: some microörganisms do the same. Experiments by Spencer[9,10] suggest that processes similar to some found in cancer occur in single-cell species exposed to carcinogens over many generations. Exposure of paramecia to methylcholanthrene enhanced the subsequent survival value and population levels, and bacteria tended to

adapt to heat when early exposure was rhythmic, but perished when it was continuous. These transformations are readily accepted as adaptive.

In the field of basic biologic investigation, notable advances have been made recently by some of our workers in tissue culture. Earle and Evans at the National Cancer Institute have worked out a technique for growing cells under a sheet of perforated cellophane, which obviates the need for a plasma clot and affords much larger cultures than were previously grown.[11]

A further accomplishment of this laboratory, by Earle and Sanford, is a procedure that allows, for the first time, the growth of an isolated cancer cell *in vitro*.[12] These techniques, in combination, make possible the growth of large cultures from a single cell, and consequently the cancer research worker can now study ample cultures of uniform cellular origin and type.

Obviously these achievements increase greatly the applicability and quantitative accuracy of tissue culture as a means of studying possible chemotherapeutic agents, carcinogenesis, and cell variation, migration and growth rate. The new techniques are already being used in an effort to define more accurately the nutrition of the cancer cell. The full potentiality of these advances, however, cannot be estimated at the present time.

A discussion of carcinogenic agents and influences may well begin with the subject of radiation, since the first experimental cancers in animals, such as Clunet[13] reported in 1910, were induced with X-rays. On the basis of numerous experiments and clinical observations, investigators agree that ultraviolet and ionizing radiations are carcinogenic. The mechanism of radiation injury is only partly understood. Experiments indicate, however, that absorption of radiation causes chemical changes detrimental to cells and tissues. The biologic effect is to some degree cumulative. And therein lies the danger of repeated exposure, even to very small doses. In studies by Lorenz and others,[14] chronic whole-body irradiation hastened the onset of cancer in mice predisposed to the disease, and late effects other than tumor production include shortening of the life span. X-ray diagnosis in the hands of a competent physician constitutes a justifiable exposure. The problem of radiation injury, however, is becoming more and more important with the increasing use of ionizing radiations in science and industry.[15]

TABLE I*—HIGHLIGHTS IN THE STUDY OF CHEMICAL CARCINOGENS

Investigator	*Contribution*
Pott (1775)	Reported soot-induced carcinomas in chimney sweeps
Yamagiwa, Ichikawa (1915)	Produced carcinoma of rabbit's ear with tar
Kennaway, Cook, Hieger (1930)	Isolated 3,4-benzpyrene from coal tar; synthesized other carcinogens
Shear, Andervont, Fieser, Lorenz, Stewart (1930—)	Studied administration and effects of carcinogenic hydrocarbons on animals of inbred strains
Wieland, Cook (1933)	Prepared 20-methylcholanthrene from desoxycholic acid
Yoshida, Sasaki (1934)	Produced hepatomas in rats with *o*-aminoazotoluene
Edwards (1941)	Produced hepatomas in mice with carbon tetrachloride
Wilson, De Eds, Cox (1941)	Noted multiple tumors in rats fed N-acetyl-2-aminofluorene
Nettleship, Henshaw (1943)	Noted that urethan increased lung tumors in predisposed mice
Berenblum (1941)	Discovered synergy of 3,4-benzpyrene and croton oil

* Material from Greenstein, J. P., *Biochemistry of Cancer*, New York: Academic Press, Inc., 1947.

Table I gives a thumbnail history of the chemical carcinogens. Sir Percival Pott is credited with the first report of industrial cancer.—During the 19th century, skin cancer was prevalent among workers in the coal tar industry; but many years passed before two Japanese workers proved experimentally that tar is carcinogenic.—The next step was to isolate a pure carcinogen, and this was finally accomplished through the perseverance of Kennaway's group in England.—As these workers produced other pure agents, a group established by Shear, under the United States Public Health Service, studied the carcinogenicity of compounds synthesized in this country, and for about a decade the two major efforts in the field overlapped.—In view of the next achievement listed (the preparation of a potent carcinogen from bile acid), one naturally wonders whether this or a similar transformation could occur in the body. Biochemists agree that *this* transformation is highly improbable; but the close structural relation of many carcinogens and

TABLE II*—HIGHLIGHTS OF TUMOR VIROLOGY

Investigator	*Source of Virus*	*Subject and Result*
Rous (1911)	Plymouth Rock hen, sarcoma	Same species, sarcoma
Ellerman (1918)	Chicken, leukemic blood	Same species, leukemia
Shope (1932)	Cottontail rabbit, papilloma	Cottontail, domestic rabbits; papilloma
Rous (1935)	Shope papilloma	Domestic rabbit, carcinoma
Bittner (1936)	Mice of high tumor strain, milk	Progeny, mammary carcinoma
Lucké (1938)	Leopard frog, carcinoma	Sames species, carcinoma of kidney
Duran-Reynals (1942—)	Rous sarcoma	Duckling and other birds; variety of tumors

* Material from Oberling, C., *The Riddle of Cancer*, New Haven, Yale Univ. Press, 1944.[16]

naturally occurring substances, such as the steroid hormones, demands that the possibility of a similar conversion be considered.

—The next three lines represent the introduction of new groups of compounds.—Urethan, mentioned in the next to the last line, offers relative simplicity of structure, a decided advantage in tracer studies of the mechanism of carcinogenesis. Larsen, studying the structure of compounds of this type in relation to biologic response, found that the simplest alterations of the urethan molecule reduced activity fully 90 per cent. Urethan administered to pregnant mice induced lung tumors in the offspring.—And lastly, we have a clear-cut example of synergistic action between a carcinogen and a noncarcinogen, a phenomenon discovered about ten years ago by Shear, who showed that the basic fraction of creosote oil accelerated skin tumor production by various hydrocarbons. Berenblum, now at the National Cancer Institute on a Special Fellowship, has shown that the appearance of cancer in mice following application of benzpyrene, the 'initiator,' is markedly accelerated by croton oil, a noncarcinogen acting as 'promoter.'

Over the years much thought has been spent in searching the chemical and other carcinogens for a characteristic structure or mode of action—in short, a 'common denominator.' Perhaps the oldest and most

familiar deduction is the 'irritation hypothesis,' extant today in modified forms. The chemical carcinogens especially have been subjected to this analysis, which largely accounts for their multiplicity; but by and large, they remain in structurally unrelated groups. In recent years, emphasis in the search for a common denominator has shifted to the cell.

Table II outlines the study of virus tumors. Rous was among the first to succeed in transmitting cancer from one animal to another by means of a cell-free filtrate.* The Rous agent has increased in virulence with subsequent transfers, and will now induce cancer in chickens within five days after inoculation, about ten times as rapidly as the most effective of other carcinogens.—Ellerman, using filtrates of sera from fowl, transmitted leukemia within the species.†—The benign virus tumor found by Shope in the wild rabbit—was shown by Rous, Beard and Kidd to become malignant in domestic rabbits.—Next in the table is Bittner's demonstration that mice of a strain in which mammary carcinoma is ordinarily frequent develop few tumors if nursed by mice of a low-tumor strain, indicating that a factor of mammary tumor development in mice is transmitted by the milk. The history of the milk agent is too long and involved to review at this time.

—To my knowledge, the tumor of the frog shown by Lucké has not been transmitted by a cell-free inoculum, but results were obtained with grafts killed by storage in glycerol.—Lastly, Duran-Reynals's studies in virus variation: showing, for example, that the Rous agent, though innocuous to ducks, will 'take' in ducklings, and when recovered from a late tumor will then take in ducks, but will have lost capacity to induce cancer in chickens. In short, a tumor virus specific for one species may become specific for another, if closely related. It will be noted that in every example in the table (except that of the milk factor in mice) inoculation has been necessary to transfer the disease.

Round shadow-casting particles, believed to be viruses of the Shope papilloma, have been photographed by Kahler and others with the electron microscope. This agent cannot be recovered from the carcinoma it induces in the rabbit, though serologic methods have demonstrated its presence. It is said to be 'masked.' At present, one objective in tumor virology is to develop unmasking techniques, which would then be applied to other tumors in an effort to reveal a virus if one exists.

* Fujinami and Inamoto, at about the same time, reported cell-free transmission of a myxosarcoma of fowl.

† A similar disease in fowl, a malignant leukosis, is also attributed to a filterable agent, and recent studies by the U. S. Department of Agriculture indicate that leukosis may be contagious in birds.[17]

TABLE III*—HIGHLIGHTS OF TUMOR ENDOCRINOLOGY

Investigator	*Contribution*
Marie (1886)	Associated cases of acromegaly with pituitary tumors
Loeb, Lathrop (1919)	Prevented mammary tumors in mice by ovariectomy
Lacassagne (1932)	Induced mammary tumors in mice with pure estrogen
Nathanson, Andervont (1939)	Prevented mammary tumors in adult female mice with androgen
Huggins (1940)	Treated prostatic carcinoma in men by control of androgen
Woolley, Little (1943)	Noted sex organ development through adrenal compensation in castrated mice
Biskind, Biskind (1944)	Noted development of tumors in rat ovary transplanted to spleen
Hertz, Tullner (1948)	Demonstrated quantitative interdependence of hormones and a vitamin in tissue growth

* Material from Greenstein, J. P., *Biochemistry of Cancer.* New York, Academic Press, Inc., 1947.

The Rous agent, because of its rapid, apparently direct action, is particularly useful in studies of carcinogenesis. Effective methods for quantitative assay of the agent have been worked out by Bryan at the National Cancer Institute.[18] But a major obstacle remains—the lack of a method for extracting pure virus, needed for studies of mechanism. To develop such a method is a major objective in tumor virology today.

Now, in view of the fact that cancer research is ultimately concerned with human cancer, we may rightly ask: Why this deep interest in the virus tumors of animals? Simply because they offer valuable material for studies of carcinogenesis, which is probably a manifestation of the same intracellular derangement whatever the agent or species. In passing, let me emphasize that there is no accepted evidence of a virus cancer in man.

Table III lists some of the highlights of tumor endocrinology.* Pierre Marie, in associating a disease of endocrine origin with tumors of the pituitary, introduced a broad area of study and an important aid in cancer diagnosis. It was later established clinically that removal of an

* The material in this table, unless otherwise noted, is from Greenstein, *Biochemistry of Cancer.*[19]

endocrine gland tumor would often correct abnormalities of development.[20]—Through use of mice predisposed to mammary cancer, Loeb and Lathrop demonstrated a hormonal factor in carcinogenesis, placing tumor endocrinology on a sound experimental basis.—In connection with the next study listed, it should be mentioned that Allen and Doisy were the first to isolate a pure sex hormone.—Nathanson and Andervont, by injecting androgen, reduced the incidence of tumors in estrogen-developed tissues; and Nathanson, Haddow, Adair and others subsequently showed the value of steroid hormones in the treatment of breast cancer.

—This work of Huggins is a triumph of biochemistry as well as endocrinology. After appropriate preliminary studies on dogs, Huggins, Stevens and Hodges succeeded in controlling, at least in a limited way, prostatic cancer in men by means of castration or estrogen administration. Moreover, the acid phosphatase levels of the sera, as shown by the Gutmans and others as well as by Huggins, proved to be highly accurate indices of case progress. Most patients are improved, and many show marked and prolonged remissions of primary and metastatic lesions.

—In the next study listed, the castrated mice developed a high incidence of adrenocortical carcinoma.—In the next study, the tumors were attributed to stimulation of the ovary by pituitary hormone, an effect normally counteracted by estrogen, which in this case was inactivated in the liver.

—Hertz and Tullner, at the National Cancer Institute, have demonstrated that folic acid is required for normal growth response to estrogen, and that folic acid antagonists can inhibit growth of estrogen-stimulated tissues. Dietary manipulations produced a 40-fold differential in estrogen-induced growth of the chick genital tract.[21]

When viewed chronologically these isolated achievements elude interpretation. I believe, though, that the findings warrant the following generalizations: first, some tumors are functional with regard to hormonal production or response; second, tumors may be induced, prevented or controlled by hormonal manipulation; third, derangement of endocrine relations within the body may result in cancer; and fourth, tissue growth normally supported by hormones may be inhibited by antagonists. Thus the importance of endocrinology in the etiology, diagnosis, and treatment of cancer is plainly revealed.

Dietary manipulations have been shown to exert pronounced effects

on carcinogenesis in animals. Caloric or amino acid restriction prevents or delays the appearance of a variety of tumors,[22] and choline deficiency, on the other hand, results in the development of hepatomas in the rat.[23] It is doubtful that these observations are of immediate practical value: the cancer-preventing diets abolish breeding capacity, and choline occurs in a wide variety of foods. As leads in cancer research, however, these and similar findings are highly encouraging and offer many suggestions for further studies. In one promising line of investigation, chemical carcinogens are administered to animals in conjunction with dietary manipulations, permitting precise control of two variables. In these studies the azo dyes are especially useful, since their action is known to be a function of diet.[24]

The effect of dietary alterations on human tumors already established has been relatively small in the few studies completed to date. In some animal experiments, however, alternate restriction and supply of a vitamin, such as riboflavin or pantothenic acid, has appreciably prolonged life, and further investigation is indicated.[25] Intensive studies on animals and selected cancer patients are needed before the role of nutrition in the control of cancer can be established.

In discussing the genetic influence in cancer, I will try to interrelate some of the material already published in this field. I believe that an understanding of the role of genetics in cancer must begin with a sound concept of the gene-character relation. Strictly speaking, a character, such as hair color, height, or color blindness, is not inherited. Its development is a result of the action of an inherited gene, or complex of genes, in a particular environment. The gene is a constant; the environment, a variable; the character, a product of the two. Stated otherwise, genes determine susceptibility to character formation; and with respect to cancer, may be said to establish, in every person, a threshold of susceptibility to the disease. The effective environment in character formation may include intra-uterine factors, diet, occupational influences—any condition, in fact, to which the individual is exposed; and it may include, secondarily, physiologic factors affecting cells. In plain words, then, cancer is not inherited, but a degree of susceptibility to it is.[26] And the adverse environment, whether that of the individual or a susceptible cell, is not beyond control.

The immediate questions confronting the geneticist in cancer re-

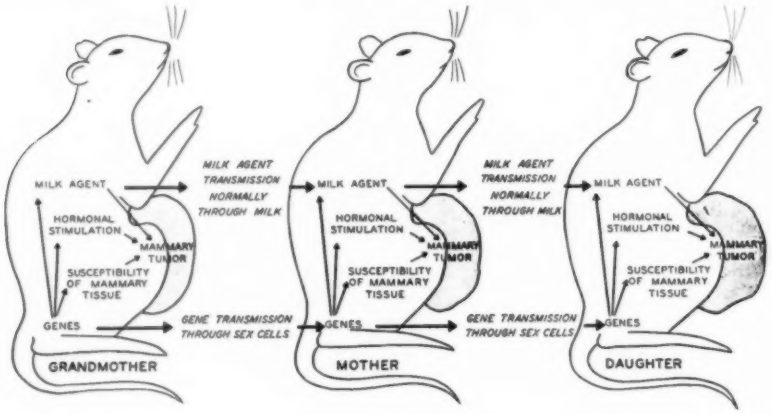

Figure 1—Relation of genes to other factors of mammary tumor development in the mouse

search are these: What are the genetic factors involved in carcinogenesis? To what environmental factors are they related? and By what physiologic paths do the genes function? For the most part, the problem is approached through studies with plants and lower animals, a practice well-grounded on the fact that the laws of genetics are among the most widely applicable in the field of biology. And of course the breeding rate must also be considered in studies involving several generations. An example of a lower form that has proved valuable as study material is the bread mold *Neurospora crassa*, which Beadle,[27] Tatum and others have used to disclose genetically controlled enzyme systems essential to the manufacture of protoplasmic constituents. Another useful species in cancer research is the common fruit fly [*Drosophila melanogaster*].

The most widely used subjects, however, are the mice of inbred strains, for which we are mainly indebted to the foresight of C. C. Little and the perseverence of L. C. Strong. Through inbreeding with selection over many years, geneticists have developed strains with high, predictable rates of cancer—mammary, lung, liver, etc.—and other strains in which tumors are infrequent. A high percentage of all cancer research requires these standardized experimental animals.

I have said that most cancers are not attributable to known carcinogens. This statement is more obviously applicable to tumors other than

mammary that arise in these mice, whose external environment throughout life is apparently normal—that is, noncarcinogenic. We may assume that these mice have a high concentration of genes favorable to tumor development; but cancer is the product of genes and environment. How, then, can we explain that the over-all incidence of cancer in some strains may be higher than 80 per cent? Speaking generally, suspicion centers on the following possible environmental factors: one, a transmissible agent, of external or internal origin; two, a carcinogenic constitutional pattern, perhaps a result of intra-uterine effects on organization; and three, a combination of these.

Such a combination has been shown to constitute the effective environment in mammary tumor production in the mouse. Figure 1, prepared from material developed by Heston, represents the genes as determinants of the constitutional pattern as well as the susceptibility of the mammary tissue.[28] The cancer-predisposing constitution, in itself a product of genes and environment, operates in this case through hormonal stimulation of the tissue and propagation and transmission of the milk agent. It is highly encouraging that cancer in these mice, though the genetic influence is strong, can be prevented by foster nursing or endocrine control.

The question naturally arises, To what extent can these genetic findings be applied to cancer in man? On the basis of these and other studies, we can certainly say that hereditary factors are involved, and that these are related to environmental factors.[29] Perhaps our most important gain from this work is a conception of the probable nature of the carcinogenic influences in human cancer of unknown etiology.

We have all heard, but it bears repeating, that there is no evidence for a milk agent in human beings. Indeed, there is statistical evidence against it, in that studies have failed to reveal a higher incidence of breast cancer among the female ancestors of mothers than among those of fathers of breast cancer patients.[30] At present, practical application of our knowledge of the milk agent is not indicated. But the search for similar factors in human cancer must be continued.

Since man is not inbred, nor reared under laboratory conditions, one cannot predict—even if both parents have cancer of the same organ—whether the offspring will develop the disease. The genetic factors of most types of cancer are probably multiple. This and practical difficulties preclude eugenic control.[28] Further genetic studies, however,

may disclose environmental and hereditary factors of cancer in man as they have in animals.

The development of genetically pure strains of mice, tumor transplantation techniques, and dependable means of inducing experimental cancer has made possible the productive application of biochemical methods in cancer research. In little more than a decade, biochemical analysis, performed against a background of biology, biophysics, pathology and other disciplines, has greatly contributed to an understanding of the properties of tumors and the tumor-bearing host. Whereas previous investigation was largely concerned with describing tissues in terms of composition, present biochemical studies emphasize the elucidation of tissue function—in a word, metabolism. And in view of the fact that cancer is a problem of growth, the importance of the new science in cancer research is manifest.

I shall attempt only to touch upon some of the major areas of activity in this field. Emphasis is placed upon those aspects of metabolism that would seem instrumental in the origin or maintenance of neoplasia: namely, enzyme activity, which underlies and effects the metabolic processes; protein synthesis, which in tumors is obviously excessive; carbohydrate utilization, which is glycolytic and hence supplementary; and the role of nucleic acid, which is associated with cellular reproduction.

With regard to enzyme activity, it may be said that every type of tissue is equipped with a characteristic pattern of enzymes, which serve as catalysts in metabolic reactions. The enzyme patterns of normal tissues are highly differentiated and vary markedly from one tissue to another. Greenstein has shown that in tumors, on the other hand, the patterns tend to be undifferentiated and nearly uniform, resembling those of the normal embryo.[6] This may explain how tumor tissue, though apparently devoid of a special 'cancer enzyme,' is geared for speed. Fundamental enzymology must be emphasized in any comprehensive program of cancer research.

In the study of tumor metabolism, untold possibilities are afforded by the recently developed techniques of tracing tissue components tagged with stable or radioactive isotopes. The major objective in tracer studies of protein synthesis is to explain the mechanism whereby substances that enter the metabolic processes are utilized in the formation of tumors. Normally, the ratio between the anabolic and catabolic

processes of a given tissue bears an orderly relation to that of all other tissues. In cancer, on the other hand, this relation is disturbed. Is this the result of a deficient control mechanism, or of evasion of this mechanism through novel avenues of synthesis? If such avenues exist, tracer methods may reveal them. Then chemotherapeutic methods may be found to block them.

In the metabolic process whereby energy is derived from carbohydrate, cancer tissue, in contrast with resting nonproliferating tissue, represents a shift toward the anaerobic. In other words, the economy tends to be glycolytic, as in a cell whose oxygen or respiratory system is inadequate.[31] Warburg, the first to note this, ascribed it to a defect in the cancer cell.[32] In recent studies by Salter, Burk and others, the respiration rate of normal tissue slices increased far more than that of tumor slices when a suitable substrate, such as succinic acid, was supplied; and thus the tumor tissue was shown to have the lower oxidative capacity, confirming Warburg's interpretation. One is reminded that Warburg, in his classic studies, went another step and attributed cancer to interference with the respiration of growing cells.[32] But this is still an open question.

In recent studies by Hogeboom, Schneider and others, appropriate tests applied to cell fractions, isolated by centrifugation, demonstrated that essential respiratory enzymes, including cytochrome oxidase, are located on the mitochondria.[33]

It is interesting that these cytoplasmic particles, the mitochondria, undergo pathogenic mutation in plants,[34] show morphologic changes in tumors,[35] and contain nucleic acid.[36]

The following observations among others suggest a relation between nucleic acid and the origin and maintenance of cancer. All known duplicating units such as chromosomes, plastids and viruses contain ribose, desoxyribose or both kinds of nucleic acid in high concentrations; and ribose nucleic acid is high in certain cytoplasmic particles of virus size.[37] Moreover, studies such as those of Griffith and later Avery show that a nucleic acid is capable of invoking permanent cellular variations. In Griffith's experiment, one type of pneumococcus was transformed into another by contact with heat-killed organisms of the second type;[38] and Avery demonstrated that desoxyribose nucleic acid was the agent of the mutation.[39] Such observations suggest innumerable questions, of which a few may be raised in passing. What is the role of nucleic acid in the

synthesis of protein? What is its role in cytoplasmic particles such as microsomes and mitochondria? Is nucleic acid the active principle of a cancer virus? Does alteration of nucleic acid represent the long-sought 'common denominator' of carcinogenesis? Only further, intensive investigation can provide the answers.

The research attack upon cancer is launched on two main levels: the gaining of basic knowledge, with a long view toward practical application; and the search for improved methods of prevention, diagnosis and treatment in the absence of an adequate explanation of the cancer process. In facing the cancer problem, we are encouraged by the fact that in many diseases the cause was unknown at the time the fight was won. I should like now to discuss briefly research in cancer therapy.

For the past three years we have heard a great deal about the therapeutic use of radio-isotopes. The isotopes most thoroughly tested against various forms of human cancer have been radioactive phosphorus [P^{32}] and sodium [Na^{24}], for whole-body radiation, and radio-iodine [I^{131}] for cancer of the thyroid. In leukemia, treatment with radio-phosphorus has produced less radiation sickness than X-ray, but has not proved superior in prolonging life.[40]

Before the radio-isotope can come into its own, means must be found for localizing these agents within the tumor, for the primary and metastatic cancer cells must receive many times as much radiation as the normal cells to warrant the treatment. Therapeutic doses must be administered with extreme caution. In several cases, such doses have been followed by aplastic anemia; and though insufficient time has passed to observe long-term effects, the dangers of radiation are well known. In clinical work involving localization of radio-isotopes in tumors, each treatment should be preceded by a small tracer dose, to determine whether adequate concentration in the tumor may be expected. Greater effort must be made to develop radioactive compounds with a high degree of tumor specificity. Until this is accomplished, the ultimate value of radio-isotopes in the treatment of cancer cannot be estimated.

During the late war, a class of compounds known as nitrogen mustards, which are closely related to mustard gas, were found to produce nuclear damage in cells. Subsequent investigation revealed that proliferating cells are most vulnerable.[41] From clinical data obtained so far, the nitrogen mustards seem to deserve a place in the treatment of

Hodgkin's disease, polycythemia, lymphosarcoma, and perhaps some cases of chronic leukemia. In these conditions, temporary remissions of varying duration have been observed. But it must be emphasized that these agents are highly toxic, and insufficiently selective to be curative. Other compounds within this class are being synthesized and tested.

Urethan [ethyl carbamate], long known as a hypnotic, has been found effective in chronic myelogenous leukemia and, to a lesser degree, in similar conditions.[42] In early cases, remissions lasting a few months may be obtained, but when the drug is discontinued, sudden relapse occurs. In advanced cases, this agent is inferior to radiation. I have mentioned that urethan induces pulmonary tumors in mice.

The compounds stilbamidine and pentamidine have been shown by Snapper and others to have some effect in multiple myeloma.[43] In conjunction with a low protein diet, these agents relieve pain and temporarily retard the disease. This is another indication that the cancerous cells most susceptible to damage are those of the blood or blood-forming organs.

In recent years a rational therapeutic principle has emerged from experiments with microörganisms—the principle of metabolite antagonism.[44] A *metabolite* may be regarded as a substance involved in the process of cellular growth and maintenance; an *antagonist*, a substance capable of interfering with the synthesis, utilization or function of a metabolite. An example of a metabolite is the vitamin folic acid; an antagonist to this, aminopterin. And under these definitions, one could include as metabolites the amino acids, enzymes and hormones. Several groups of compounds are being tested in laboratories and hospitals for possible antagonistic effect in the growth or maintenance of malignant cells.

In studies by Farber and others, folic acid antagonists have produced temporary remissions in a few children with acute leukemia.[45] At the National Cancer Institute, Law has obtained remissions in leukemic mice.[46] But these agents, too, are highly toxic, and are not recommended as yet for general use by the practitioner. Results to date, however, should encourage further investigation of these and other metabolite antagonists, especially in controlled experiments with animals. The underlying principle is sound and well worth pursuing.

I have mentioned the value of estrogen in the treatment of cancer of the prostate, and of androgen or estrogen in breast cancer. The

Therapeutic Trials Committee of the American Medical Association has undertaken the task of determining the optimal use of hormones in breast cancer therapy.[47] I shall not discuss the subject further, except to emphasize that to date hormonal treatment in cancer has been palliative only.

Another promising approach to the development of chemical agents for cancer therapy is the systematic screening of compounds known to damage cells. In this approach, it is initially recognized that the vulnerability of cancer tissue to an agent has always been shared by normal tissues. This is turned to advantage: known cytotoxic compounds are searched for those especially destructive to cancer cells; and as such agents are found, they are subjected to chemical modification designed to reduce toxicity or increase activity.

In a screening program under the direction of Shear at the National Cancer Institute, this is essentially the guiding principle in the selection of compounds for testing.[48] The workers represent a variety of scientific disciplines. Their concerted purpose is to find or develop chemical agents that either alone or combined with radiation or surgery will control tumors without prohibitive destruction of normal tissue.

Sarcoma 37 in the mouse is used in the preliminary screening of every compound. Transplanted tumors may be considered as artificially established, standardized metastases. Fifteen mice are used in the first testing of each agent.

So far, more than a thousand agents have been screened, and the results have far exceeded expectations. At a single dose near the lethal, definite tumor damage has been obtained in the last few years with about sixty compounds.[49]

Although none of the sixty positive compounds completely destroys the test cancer, the results show decided progress, not only in providing agents for further study but in proving the value of a screening method in experimental cancer chemotherapy. We propose to continue the screening procedure. Moreover, the positive agents will be tested against several forms of cancer in various laboratory animals. On the basis of findings to date, the structures of effective compounds are being studied in terms of function, with a view to producing, through alteration of the original molecule, an agent safe for the host but fatal to the tumor.

This brief review of studies in cancer therapy does not purport to reflect the large amount of effort invested in this field. I have tried only

to indicate that there is such an effort, and to emphasize, to my deep regret, that no cure except surgery or radiation is as yet available. This is not to say, however, that highly encouraging results are lacking. In this difficult problem, we now appreciate that a concerted attack, based on sound scientific principles and following practical systematic lines of approach, is our best assurance of success. In laboratories and hospitals throughout the country, such an attack is under way.

Another approach that has yielded valuable information and is being intensified in cancer research programs is epidemiology. This term is used to designate investigation of the incidence of cancer by types and site with relation to total history including environment. This extension of the term 'epidemiology' is largely due to similarities of method to those used in the study of communicable disease. In cancer research, epidemiologic methods have contributed especially to our knowledge of causal factors in the environment of industrial workers.

Studies to identify environmental factors of carcinogenesis in industry and to develop means of controlling them usually proceed in four major steps. First, mortality rates by geographic region are searched for areas of high incidence. Second, the hazardous areas are searched for evidence of possible carcinogens, such as unusual industrial products. Third, the suspected agent is tested in the laboratory. If found carcinogenic, the fourth step is taken: measures are devised for protecting the workers and community. These steps, though not always applied in formal programs, have exposed a formidable host of carcinogenic agents and influences, including the following industrial materials: tar, shale oil, crude paraffin, creosote, crude anthracene, arsenic, benzol, chromates, asbestos, intermediates of aniline dyes, and the energy agents already mentioned.[50] At the National Cancer Institute, a program under the direction of Hueper has been established to detect other agents and to advise and assist industries in eliminating the hazards.

Another epidemiologic approach is to follow special population groups, in order to determine whether certain influences, such as a given diet or habit, will contribute to carcinogenesis. A familiar example of a habit that leads to cancer is the chewing of betel nut quids in Asiatic countries.[50] At present, strong clinical impressions indicate that groups with certain pathologic conditions, such as achlorhydria and pernicious anemia, should be traced with a view to deciding whether the incidence of cancer in these groups is higher than average. A major advantage of

such a program is the contribution to early case finding.

In coöperation with the University of Washington in Seattle, the National Cancer Institute is engaged in laboratory and clinical studies to develop a diagnostic test or tests for cancer. At present, tests reported in the literature are being evaluated through application to cancer patients and persons with other diseases. Coöperative arrangements have been established with local hospitals and physicians. Tests found effective on the advanced cancer patients in Seattle will be tried for mass-screening possibilities at the venereal disease clinic of the United States Public Health Service Medical Center in Hot Springs, Arkansas. The possibility that available material would yield a practical means of segregating persons for further examination should be thoroughly explored.

In this discussion I have not attempted to divide the subject matter by scientific disciplines, since cancer research, for the most part, is conducted on an 'interdisciplinary' basis. This tendency to transcend departmental barriers represents an important advance. In the past, outstanding contributions were made in isolated fields, such as pathology, physics and surgery, to which must be credited, respectively, microscopic examination of tissue, which remains the most reliable method of cancer diagnosis, and radiology and radical excision, the only cures. Now that a groundwork has been laid, however, those disciplines are drawn upon by others, which build in turn an indispensable foundation.

A voice from antiquity bespoke the interdisciplinary approach: Bacon said: "The strength of all sciences, which consists in their harmony, each supporting the other, is as the strength of the old man's fagot in the band; for were it not better to set up one great light, or branching candlestick of lights, than to go about with a small watch candle into every corner?" James Ewing was among the first to conceive of a cancer institute in the modern sense—as an institution where scientists of many disciplines combine their efforts and resources in a common mission, cancer research. In the future an even closer integration of disciplines must be achieved.

Integration of laboratory and clinical investigation in cancer is requisite throughout the country. At the National Institutes of Health, this need will be met with the completion of the new Clinical Center, in which 100 beds will be used for cancer patients. Ground is now being prepared for the buildings, which are expected to be completed in about

two years. The Center will make possible direct application of basic findings, and will help meet the national need for clinical cancer studies.

This general view of cancer research may warrant a general conclusion. From the facts gleaned in recent years, through much profound thought and unremitting toil in laboratories and clinics throughout the world, one may deduce that cancer, contrary to the word of some discouraged early workers, is not an unsolvable mystery of the universe. It is a practical scientific problem, and science in its stride can conquer it. But the problem, I repeat, is subtle; the solution may not come soon; and the attack, at least for the present, must include much basic investigation and must advance on a broad front.

I should like to close on a note of caution. The people of the world have a vital stake in the progress of cancer research, and are entitled to full and fair reports of scientific accomplishment. Because of the great eagerness of the public for news that cancer research is 'on the right track,' that the long-sought cure is at hand or close to it, reports of moderate advances are frequently exaggerated. Because the wish is father to the thought, hopeful new leads may be mistaken for fully developed answers to major questions.

The penalty of exaggeration is disillusionment. Our outlook in cancer research is optimistic; all of us hope that the solutions to the problems are not too far off, and there is no reason to believe that they are. But the available evidence does not necessarily indicate that the solutions are right around the corner. The distance ahead, as well as a balanced interpretation of achievements, must be emphasized in every progress report.

A concerted attack on cancer is being made today through the efforts of universities, general and cancer hospitals, voluntary organizations such as the American Cancer Society, and of Federal agencies such as the National Cancer Institute and the Atomic Energy Commission. Through continued support of these efforts as long as necessary, by a generous and confident nation, the cancer problem will be solved.

REFERENCES

1. Ashford, C. A. and Dixon, K. C. Effect of potassium on glycolysis of brain tissue with reference to Pasteur effect, *Biochem. J.*, 1935, *29*:157.
2. Spencer, R. R. Problems of cancer biology, *J.A.M.A.*, 1945, *127*:509.
3. Chalkley, H. W. et al. *Conference on the mechanisms of cell division*, New York Academy of Sciences, May 1948.
4. Porter, K. R., Claude, A. and Fullam,

F. F. Study of tissue culture cells by electron microscopy, *J. Exper. Med.*, 1945, *81*:233.

5. Ewing, J. *Lectures on tumor pathology.* New York, Cornell Univ. Medical Schooi, 1933, p. 13.
6. Greenstein, J. P. *Biochemistry of cancer.* New York, Academic Press, Inc., 1947, p. 13.
7. Rose, S. M. Epidermal dedifferentiation during blastema formation by regenerating limbs of *Triturius viridescens*, *J. Exper. Zool.*, 1948, *108*:337.
8. Fischer, A. *Biology of tissue cells.* New York, G. E. Stechert & Co., 1946, Chapt. 2.
9. Spencer, R. R. and Melroy, M. B. Survival value of methylcholanthrene-adapted paramecium, *J. Nat. Cancer Inst.*, 1940-41, *1*:343.
10. Melroy, M. B. and Spencer, R. R. *J. Nat. Cancer Inst., in press.*
11. Evans, V. J. and Earle, W. R. Use of perforated cellophane for the growth of cells in tissue culture, *J. Nat. Cancer Inst.*, 1947-48, *8*:103.
12. Sanford, K. K., Earle, W. R. and Likely, G. D. Growth in vitro of single isolated tumor cells, *J. Nat. Cancer Inst.*, 1948-49, *9*:229.
13. Clunet, J. *Recherches expérimentales sur les tumeurs malignes.* Paris, Steinheil, 1910.
14. Lorenz, E., Heston, W. E., Eschenbrenner, A. B. and Derringer, M. K. Plutonium project; biological studies in tolerance range, *Radiol.*, 1947, *49*:274.
15. Lea, D. E. *Actions of radiations on living cells.* New York, Macmillan Co., 1947.
16. Oberling, C. *The riddle of cancer.* New Haven, Yale Univ. Press, 1944, chapts. 4 and 5.
17. Waters, N. F. Natural transmission of avian-lymphomatosis, *Poultry Science*, 1945, *24*:226.
18. Bryan, R. Quantitative studies on the latent period of tumors induced with subcutaneous injections of the agent of chicken tumor, *J. Nat. Cancer Inst.*, 1945-46, *6*:225; 373.
19. Greenstein, J. P. *Biochemistry of cancer.* New York, Academic Press, Inc., 1947, chapt. 6.
20. Selye, H. *Textbook of endocrinology.* Montreal, Canada, Univ. of Montreal, 1947.
21. Hertz, R. and Tullner, W. W. Quantitative interference with estrogen-induced tissue growth by folic acid antagonists, *Endocrinology*, 1949, *44*:278.
22. White, J., White, F. R. and Mider, G. B. Level of protein ingestion and an appraisal in terms of protein composition, *Ann. New York Acad. Sc.*, 1947-48, *49*:41.
23. Engel, R. W., Copeland, D. H. and Salmon, W. D. Carcinogenic effects associated with diets deficient in choline and related nutrients, *Ann. New York Acad. Sc.*, 1947-48, *49*:49.
24. Kensler, C. J., Sugiura, K., Young, N. F., Halter, C. R. and Rhoads, C. P. Partial protection of rats by riboflavin with casein against liver cancer caused by dimethylaminoazobenzene, *Science*, 1941, *93*:308.
25. Morris, H. P. Some nutritional factors influencing the origin and development of cancer, *J. Nat. Cancer Inst.*, 1945-46, *6*:1.
26. Heston, W. E. Role of heredity in tumor development, *J. Nat. Cancer Inst.*, 1944-45, *5*:161.
27. Beadle, G. W. Biochemical genetics, *Chem. Rev.*, 1945, *37*:15.
28. Heston, W. E. Paths of gene action in mammary-tumor development in mice, *J. Nat. Cancer Inst.*, 1946-47, *7*:79.
29. Heston, W. E. Role of heredity in tumor development, *J. Nat. Cancer Inst.*, 1944-45, *5*:161.
30. Jacobson, O. Cited by Kemp, T. Heredity in human cancer, *Brit. J. Cancer*, 1948, *2*:144.
31. Greenstein, J. P. *Biochemistry of cancer.* New York, Academic Press, Inc., 1947, p. 297.
32. Warburg, O. *The metabolism of tumors.* London, Constable & Co., 1930.
33. Hogeboom, G. H., Schneider, W. C. and Palade, G. E. Cytochemical studies on mammalian tissues, *J. Biol. Chem.*, 1948, *172*:619.
34. Woods, M. W., duBuy, H. G., Burk, D. and Hesselbach, M. L. Cytological stud-

ies on the nature of the cytoplasmic particulates in . . . melanoma, *J. Nat. Cancer Inst.*, 1948-49, *9*:311.

35. Dalton, A. J. Symposium on mammary tumors in mice, *Publications of Am. Assoc. for Advancement of Science*, 1945, p. 7.
36. Hogeboom, G. H., Schneider, W. C. and Palade, G. E. Cytochemical studies on mammalian tissues, *J. Biol. Chem.*, 1948, *172*:619.
37. Spiegelman, S. and Kamen, M. D. Some basic problems in the relation of nucleic acid turnover to protein synthesis, *Cold Spring Harbor Symposia on Quantitative Biol.*, 1947, *12*:211.
38. Boivin, A. Direct mutation in colon bacilli, by an inducing principle of desoxyribonucleic nature, *Cold Spring Harbor Symposia on Quantitative Biol.*, 1947, *12*:7.
39. Avery, O. T., MacLeod, C. M. and McCarty, M. Studies on chemical nature of substance inducing transformation of pneumococcal types, *J. Exper. Med.*, 1944, *79*:137.
40. Reinhard, E. H., Moore, C. V., Bierbaum, O. S. and Moore, S. Radioactive phosphorus as a therapeutic agent, *J. Lab. & Clin. Med.*, 1946, *31*:107.
41. Wintrobe, M. M., Huguley, C. M., Jr., McLennan, M. T. and de Carvalho Lima, L. P. Nitrogen mustard as therapeutic agent for Hodgkin's disease, lymphosarcoma and leukemia, *Ann. Int. Med.*, 1947, *27*:529.
42. Paterson, E., Thomas, I. A., Haddow, A. and Watkinson, J. M. Approaches to tumor chemotherapy, *Publications of Amer. Assoc. for Advancement of Science*, 1947, p. 401.
43. Snapper, I. Stilbamidine and pentamidine in multiple myeloma, *J.A.M.A.*, 1947, *133*:157.
44. Roblin, R. O. Metabolite antagonists, *Chem. Rev.*, 1946, *38*:255.
45. Farber, S., Diamond, L. K., Mercer, R. D., Sylvester, R. F. and Wolff, J. A. Temporary remission in acute leukemia in children produced by folic acid antagonist, *New England J. Med.*, 1948, *238*:787.
46. Law, L. W. *Cancer Research, in press.*
47. Council on Pharmacy and Chemistry. Estrogens and androgens in mammary cancer, *J.A.M.A.*, 1947, *135*:987.
48. Shear, M. J., Hartwell, J. L., Peters, V. B., Dalton, A. J. and Dunn, T. B. Approaches to tumor chemotherapy, *Publications of Am. Assoc. for Advancement of Science*, 1947, p. 236.
49. Shear et al. Am. Assoc. for Cancer Research, 1949.
50. Hueper, W. C. *Occupational tumors and allied diseases.* Springfield, Ill., C. C. Thomas, 1942.

AN EVALUATION OF THE SURGICAL TREATMENT OF HYPERTENSION*

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In a discussion of the surgical treatment of hypertension, three procedures should be mentioned, unilateral nephrectomy, the removal of adrenal tumors, and sympathectomy.

Unilateral Nephrectomy: The percentage of hypertensive patients who have a unilateral renal lesion which would justify nephrectomy is very small, probably a fraction of one per cent. The statistical chance that removing such a kidney will favorably influence the course of the disorder is in the vicinity of 20 per cent according to Smith[1]. It would seem reasonable to use the same indications for nephrectomy in hypertensive patients as in non-hypertensive patients.

Adrenal Tumors: It is difficult to estimate the incidence of adrenal tumors among hypertensive patients. In those cases I have treated surgically in whom the adrenal glands were carefully inspected and palpated, the incidence was approximately 5 per cent. One tumor in ten proved to be a pheochromocytoma, an incidence of 0.5 per cent. The vast majority of the remaining tumors were cortical adenomas and with one exception did not appear to influence the hypertension materially. It is therefore apparent that adrenal tumors together with the even rarer paragangliomas are factors of importance in less than 1 per cent of hypertensive patients. Because the result of removing these tumors is almost always worthwhile, it is important that the diagnosis be made. In this connection it should be reëmphasized that although many pheochromocytomas cause paroxysmal attacks of hypertension, others produce a continued non-paroxysmal form of the disorder. To differentiate the latter group from patients having so-called essential or

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malignant hypertension may be difficult. Most of our patients have fallen into the latter category, and the tumors were discovered only because the adrenal glands were explored. Certain signs and symptoms which in retrospect would appear to be of diagnostic value have been noted. Among these are excessive sweating, postural hypotension with tachycardia, normal cold pressor response, hypermetabolism, altered peripheral blood flow, hyperthermia, and hyperglycemia. This small but interesting group of patients will be discussed in greater detail in the near future.

Operations Upon the Sympathetic Nervous System

In by far the largest number of hypertensive patients who have been treated surgically, a sympathectomy of one sort or another has been performed. The first attempt to modify the course of hypertensive cardiovascular disease by sympathectomy was made in 1924. Numerous reports have appeared in the literature since that time.[2-10] The first operation was a periarterial sympathectomy upon the left femoral artery of a young male suffering from the most severe form of the disorder, so-called malignant hypertension, in its terminal stage. This operation was performed by Adson. In the following year he operated upon a second patient, this time performing a bilateral lumbar sympathectomy. Their experiences with these two patients were discussed by Rowntree and Adson in 1925.[11]

As time has gone on, operations upon the sympathetic nervous system have become more and more extensive. Every conceivable variation has now been tried, including total sympathectomy in a few cases. I would estimate that at least 5,000 and possibly 10,000 hypertensive patients have been treated by one form of sympathectomy or another in this country during the past twenty years. At the same time, probably hundreds of thousands of patients have been treated in other ways. One might therefore think that it would be possible to evaluate one form of therapy or another with finality at this time. This, however, is not the case.

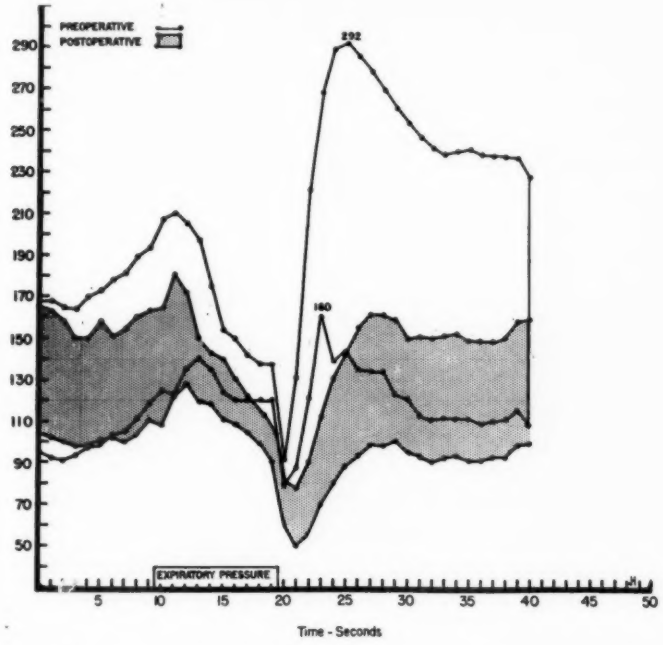
Evaluation of Splanchnicectomy—Physiologic Effects

In evaluating a therapeutic measure, consideration must be given to the nature of its effect upon the disorder in question. Any therapeutic value which sympathectomy may have is undoubtedly due

to the physiologic effects of this procedure upon the cardiovascular system. These fall into two categories,—known and presumed. Of the known effects there are two,—modification of blood pressure levels and modification of the reflex regulation of blood pressure resulting from the inactivation of important components of the vasoconstrictor mechanism. Of the presumed effects, abolition of reflex secretion of adrenin and stabilization of blood flow through the denervated vascular bed might be mentioned.

Effect of Splanchnicectomy Upon Blood Pressure Levels: Reduction in blood pressure levels varying from slight to marked, lasting from one to ten years, have followed the denervation of large vascular areas. The percentage of patients in whom significant changes in blood pressure levels have been noted varies in the different series from about 20 per cent to as high as 75 per cent. The percentage will vary because the criteria used for judging changes in blood pressure differ and because there are wide variations in the patient material and operative techniques in the different series. It has been difficult to predict just what the effect of operation upon blood pressure levels will be in unselected cases and how long it will last. Judging from my own experiences, 66 per cent of unselected patients with persistently elevated blood pressure with associated cardiovascular changes have had a slight to marked reduction in blood pressure lasting from one to five years.[12] In the five to ten-year follow-up period, 47 per cent of these same patients have had a blood pressure reduction comparable to that noted during the first five-year period.[13] This indicates a definite tendency for blood pressure to return to or towards preoperative levels with the passage of time. The great majority of patients who have had prolonged and persistent reductions in blood pressure levels have done well as judged by mortality rates and improvement in or lack of progression of cardiovascular disease. In occasional instances, cardiovascular disease has progressed in spite of marked and persistent reduction in blood pressure levels. In other cases, improvement in the status of the cardiovascular system has been noted in the absence of any demonstrable change in blood pressure levels. The favorable effect of sympathectomy does not appear to be solely dependent upon the lowering of blood pressure levels.

Effect of Splanchnicectomy Upon Reflex Control of Blood Pressure: The second known physiologic effect of splanchnicectomy is a marked alteration in the reflex control of blood pressure. This has been recently



* Fig. 1—Response to Valsalva test before and after lumbodorsal splanchnicectomy. Variations in blood pressure caused by reflex vasoconstriction are abolished when a large vascular area such as the splanchnic bed is denervated. These variations may be very marked, as in this case. This physiological effect of sympathectomy occurs regardless of whether the basal levels are altered or not and is well demonstrated by the Valsalva maneuver as in this figure. Intra-arterial blood-pressure levels are optically recorded with a Hamilton manometer before, during, and after a ten-second period of forced expiration. Before operation there was a sharp overshoot of blood pressure to very high levels within a few seconds after the expiratory period. After operation (shaded graph) the overshoot was abolished. It seems probable that the elimination of such reflex variations in blood pressure is partly responsible for the favorable changes in the cardiovascular system which may be noted after operation.

demonstrated by Wilkins et al.[14] In response to various stimuli, blood pressure levels may rise abruptly to high levels in normally innervated patients. This may be a factor of considerable importance in connection with the rate of progress of cardiovascular disease. These sudden elevations of blood pressure occur within a few seconds following stimulation. These are readily demonstrated by the Valsalva maneuver, during

* Reproduced from the British Medical Journal, 2: 237, 1948.

which intraarterial blood pressure levels are optically recorded by means of the Hamilton manometer. These reflex variations in blood pressure are almost always completely abolished following the denervation of a large vascular area. This effect occurs irrespective of changes in basal blood pressure levels and is well demonstrated by Figure 1. The effect has been shown to persist for years after operation, even in patients in whom the blood pressure has returned to or near preoperative levels. It is reasonable to believe that the prolonged abolition of marked overshoots in blood pressure due to reflex vasoconstriction would reduce the stress and strain upon the cardiovascular system.

Untoward Physiologic Effects: Among the physiologic effects of operation which are troublesome to the patients are postural hypotension with tachycardia, increased perspiration and coldness in the undenervated areas. The magnitude and duration of postural hypotension varies with the extent of the operation into the lumbar areas. Unless postural hypertension without unusual tachycardia is present before operation, it is our routine to remove the sympathetic trunks bilaterally from the eighth thoracic to the first lumbar segments inclusive. The postural hypotension after such a procedure is generally not particularly troublesome and is readily counteracted by bandages and girdles. These are usually discarded in about three months. More extensive denervations result in more prolonged postural effects. It has not been demonstrated as yet that they are indicated as a routine measure. It is most important to avoid lumbodorsal splanchnicectomy in hypertensive patients with unusually rapid heart rates. In these, postural hypotension and tachycardia may be very troublesome and disabling. A thoracic sympathectomy including the cardiac innervation but preserving the lumbar outflow is indicated in such cases. If care is taken to adjust the operative procedure to the patient, prolonged disability can be avoided without sacrificing therapeutic effectiveness. If loss of ejaculation is important, the lumbar ganglia should be preserved on one side. Increased perspiration in undenervated areas in hot weather and vasoconstriction in cold weather are unpleasant but not serious sequelae. The symptoms which are acquired as a result of the operation are usually more than counterbalanced by the improvement in symptoms present prior to operation. Of the patients who have been reëxamined 5 to 10 years after operation, 83 per cent state that the favorable effects of operation definitely outweigh the unfavorable effects. Improvement in or relief

of headaches was obtained by 92 per cent of cases. Headaches of consequence were not present in 27 per cent of cases prior to operation. Most patients return to work in the course of three to six months. This, together with the hospital stay and its associated expense, introduces an economic factor which must be considered. If on the other hand, the patient's useful life expectancy is materially increased, this factor is more than counterbalanced. It seems proper to caution against too extensive operative procedures and to emphasize the need for selecting the proper type of denervation for the individual patient. If the operation is either too extensive or inappropriate, the untoward effects will frequently outweigh the beneficial effects.

Operative Mortality and Morbidity: The operative mortality has been low considering the advanced cardiovascular changes which have been present in many patients. The operative mortality and morbidity vary with the surgical technique employed. The transthoracic approach carries the highest mortality and morbidity. In experienced hands and with careful attention to preoperative preparation, anesthesia, and postoperative care, the operative mortality should be in the vicinity of 1 per cent. Of utmost importance is the replacement of operative and postoperative blood loss. In virtually every patient it should be presumed that slow, insidious oozing will take place into the operative field during the early postoperative period. This frequently will amount to 500 cc. or more and exceeds operative blood loss in importance. This can be detected by hematocrit determinations on the third and sixth postoperative days. In all cases, particularly in those with more advanced cardiovascular disease, it is essential that blood loss be replaced and hematocrit levels be maintained.[15] This will significantly reduce operative mortality and morbidity.

As a rule, the operative procedures are carried out in two stages about ten days apart. For the lumbodorsal technique, the average hospital stay is thirty days. Transthoracic procedures are utilized by us in cases in which we wish to include the heart in the denervated area. This technique is employed in hypertensive patients having coronary heart disease with angina pectoris or in patients with tachycardia. The operations are performed two weeks apart and the total hospital stay is usually lengthened by a week or so. This technique is employed in about 20 per cent of patients and the lumbodorsal extrapleural technique in about 80 per cent. The principal source of postoperative discomfort

TABLE I

Vascular Area	*No. of Cases*	*Status 5-10 Years After Lumbodorsal Splanchnicectomy*		
		Improved	*No Change*	*Worse*
Retinal	120	41%	39%	20%
Cardiac	125	42%	49%	9%
Renal	114	29%	61%	10%
All (including cerebral)	100	51%	12%	37%

is intercostal neuritis. This can be greatly minimized by reducing operative trauma.

Effect of Sympathectomy Upon Cardiovascular Disease: Following sympathectomy, attention has been called to favorable changes which have been noted in the cardiovascular system. Most reports are concerned with patients followed for a few months to a few years. To date only two publications have dealt with more than small numbers of surgically treated patients followed for five years or more. The first was by Peet and Isberg,[16] and the second, a recent report by this author.[13] A follow-up period of at least five years seems necessary in order to begin to evaluate the effect of operation upon the cardiovascular system and to study the rate of progress of cardiovascular disease. It may be necessary to follow patients for ten or more years to evaluate this aspect of the problem accurately. Peet and Isberg reported improvement in the eyegrounds of 62 per cent of 146 patients followed for five to eleven years. Unfavorable changes were noted in 3 per cent of the cases. The remaining 35 per cent showed no change. They noted that during a similar follow-up period, 91 per cent of 80 hearts which were normal in size before operation did not change significantly, while 9 per cent became larger. Of 48 enlarged hearts, 52 per cent decreased in size, 44 per cent remained the same, and 4 per cent enlarged. Of 84 cases with normal electrocardiograms, 93 per cent showed no change and 7 per cent became worse. Of 57 abnormal electrocardiograms, 53 per cent improved, 42 per cent were unchanged, and 5 per cent were worse. Of 62 patients having normal renal function prior to operation, there was no change in 82 per cent and a reduction in 18 per cent. Of 55

TABLE II—ELECTROCARDIOGRAMS OF NON-SURGICALLY AND SURGICALLY TREATED HYPERTENSIVE PATIENTS FOLLOWED FOR 5 YEARS OR MORE

Author	*Treatment*	*No. Cases*	*Improved*	*No Change*	*Worse*
Canabal, Thomson, and White, P.D. (1945)	Non-Surgical	50	10%	40%	50%
Rasmussen and Boe (1945)	Non-Surgical	39	8%	56%	36%
Isberg and Peet (1948)	Surgical	184	19%	76%	5%
Smithwick (1948)	Surgical	125	42%	49%	9%

cases with impaired function, 36 per cent were improved, 53 per cent unchanged and 11 per cent were worse. The status of the various vascular areas of the first 100 or more cases to be followed for 5 to 10 years after lumbodorsal splanchnicectomy are summarized in Table I.

The significance of these data depends upon a comparison with similar data concerning non-surgically treated hypertensive patients followed for comparable periods of time. Unfortunately very little comparable data are available at this time. I have been able to find some information concerning the status of the electrocardiograms of hypertensive patients who were not treated surgically and who were followed for five years or more in the reports of Canabal, Thomson, and White[17] and of Rasmussen and Boe.[18] These are summarized in Table II and are compared with the most recent findings of Isberg and Peet[19] and with those which I have reported. The comparison is very much in favor of the surgical series, is very significant statistically, and suggests that the course of hypertensive heart disease as judged by the electrocardiograms has been favorably modified by surgical treatment. In Table II the statistics of four authors are compared without regard to the original status of the electrocardiograms, since these data were not available for the patients who were not treated surgically. Of the 184 cases in the Isberg and Peet series, the electrocardiograms were normal in 101 and abnormal in 83 cases before operation. There was no change in 94 per cent and an unfavorable change in 6 per cent of the normal group during the five to twelve-year period following operation. Improvement was noted in 41 per cent of the abnormal group, with no

change in 55.4 per cent and an unfavorable change in 3.6 per cent. Of the 125 cases in my series, 55 had normal and 70 abnormal electrocardiograms before operation. In the normal group, there was improvement in 14.5 per cent, no change in 80 per cent and an unfavorable change in 5.5 per cent. In the abnormal group there was improvement in 64.3 per cent, no change in 24.3 per cent and an unfavorable change in 11.4 per cent. The time of follow-up was five to ten years for the 125 cases. We have used the criteria of Canabal, Thomson and White in evaluating changes in the electrocardiograms. Because there is considerable variation in the normal range, it is possible for an electrocardiogram, originally normal, to improve.

Much more data concerning the progress of cardiovascular disease in our surgically treated patients will become available as the follow-up progresses. It is important that the data which are available concerning patients who have not been treated surgically be supplemented as soon as possible. In this conection, the following quotation from the article of Canabal, Thomson and White is pertinent. "Having become interested in these electrocardiographic changes following splanchnic sympathectomy, we sought in vain for published reports of comparable and adequate control studies, that is, studies of the evolution of the hypertensive electrocardiogram in patients without such operation. Hence, we have collected as many such data as we have as yet been able to find which were based on adequate criteria. This search has been difficult and has yielded only fifty cases."

Mortality Among Hypertensive Patients

An evaluation of the surgical treatment of hypertension should take into consideration the effect of the procedure upon the mortality rate. In the final evaluation of any therapeutic measure, its effect upon life expectancy will be the most important consideration. The mortality rates for hypertensive patients followed for four to eleven years who were not treated surgically may be judged from representative reports in the literature. Those of Janeway,[20] Blackford, Bowers, and Baker,[21] Keith, Wagener and Barker,[22] Rasmussen and Boe,[18] and Bechgaard[23] are summarized in Table III. The mortality rates vary widely in the different series, from 28 per cent to 91 per cent. Obviously, there must have been a considerable difference in the patient material comprising the various series. In the majority, the mortality was high. It becomes

TABLE III—MORTALITY AMONG HYPERTENSIVE PATIENTS NOT TREATED SURGICALLY

Author	*No. Cases*	*Time Followed*	*Mortality*
Janeway (1913)	458	1-10 years	50%— 5 years 75%—10 years
Blackford, Bowers, and Baker (1930)	202	5-11 years	50%
Keith, Wagener, and Barker (1939)	219	5-9 years	91%
Rasmussen and Boe (1945)	100	6 years	52%
Bechgaard (1946)	1,038	4-11 years	28%

TABLE IV—MORTALITY AMONG HYPERTENSIVE PATIENTS NOT TREATED SURGICALLY

Author	*Males*	*Females*
Janeway (1913)	53%	33%
Blackford, Bowers and Baker (1930)	70%	39%
Keith, Wagener, and Barker (1939)	93%	88%
Rasmussen and Boe (1945)	71%	43%
Bechgaard (1946)	41%	22%
Average	66%	45%

apparent that it is impossible to compare mortality rates for different groups of hypertensive patients unless they are divided into subgroups in which some of the important variable factors present in this disorder are held constant. Before mortality rates can be used as a measure of the value of any particular form of therapy, this must also be done. The more variables that can be controlled, the more accurate will be the conclusions. Among the many important variables are the sex of the patient, the severity of the hypertension as judged by the resting diastolic blood pressure level and the grade of eyeground change. The age factor should also be taken into consideration. About 90 per cent of the patients in my series are below 50 years of age. The majority of patients in non-surgically treated series are over 50 years of age.

TABLE V—MORTALITY AMONG HYPERTENSIVE PATIENTS TREATED SURGICALLY

Author	*Technique*	*No. Cases*	*Time Followed*	*Mortality*		
				Total	*Males*	*Females*
Peet and Isberg (1946)	Supradiaphragmatic Splanchnicectomy	437	5-12 years	42.5%	62%	30%
Smithwick (1948)	Lumbodorsal (thoracolumbar) Splanchnicectomy	317	5-10 years	29%	35%	25%

Influence of Sex Upon Mortality: The importance of the sex factor is clearly brought out by Table IV, in which the mortality rates for the male and female patients of the same authors quoted in Table III are given. It is very apparent that the mortality among males is much higher than among females, the average rate for the former being 66 per cent and for the latter 45 per cent during a comparable period of observation. It is therefore clear that in evaluating therapy, the sex factor must be taken into consideration.

The mortality rates for surgically treated patients followed from five to ten years or more are summarized in TableV. With regard to my statistics, it should be stated that during the first 5 years of the study, from October, 1938 through September, 1943, a total of 330 patients with continued hypertension and cardiovascular changes varying from slight to marked were operated upon. A bilateral lumbodorsal splanchnicectomy was performed in all of these cases. As of September 1, 1948, thirteen of the patients are untraced. This represents 4 per cent of the total material. The remaining 317 cases were operated upon at least five and at most ten years ago. Of these, 225 are living and 92 are dead, a mortality of 29 per cent. The mortality for males was 35 per cent and for females 25 per cent, again emphasizing the higher death rate among males. The difference in the mortality rate for the two sexes, however, was not nearly as great as in those cases who were not treated by lumbodorsal splanchnicectomy. These statistics are included in Table V, which also contains comparable data from the Peet and Isberg series. The over-all mortality differs in the two series, that for male patients being much lower in the lumbodorsal series. The

TABLE VI—MORTALITY AMONG HYPERTENSIVE PATIENTS
Six Years after First Examination or 5 to 10 Years after Operation

Resting Diastolic Level	*Rasmussen and Boe*			*Smithwick*		
	No. Cases	*No. Deaths*	*Mortality*	*No. Cases*	*No. Deaths*	*Mortality*
90-109	46	20	43%	80	5	6%
110-124	31	18	58%	98	24	25%
125+	19	14	74%	139	63	45%

mortality rates for both males and females are considerably lower in the lumbodorsal series than the average for the cases not treated surgically.

Mortality According to Resting Blood Pressure Level: The blood pressure level of a particular hypertensive patient is difficult to evaluate. There is no generally accepted method for determining this figure. Many authors utilize ambulatory blood pressure data. Because of the fact that ambulatory pressures may be elevated and resting pressures much lower or within the normal range we have felt that it was preferable to use resting levels. There is no unanimity of opinion as to what constitutes a resting level. Some authors feel that a rest period of many days or even weeks is desirable. Our plan has been to have the patients rest for forty-eight hours in order to detect patients with transient or intermittent hypertension. Patients with diastolic levels below 90 resting and over this figure when active are classified as having transient or intermittent hypertension. We have operated upon a few such cases and they will be reported separately. Patients with resting diastolic levels of 90 m.m. or more are regarded as having persistent hypertension. This report deals with such cases. While it is undoubtedly true that the disastolic levels of some cases would fall to lower levels with a longer rest period, we have felt that rest beyond a certain point becomes a therapeutic measure and for practical purposes is not as satisfactory as a short rest period for differentiating between transient and persistent hypertension. Prolonged bed rest would, however, differentiate between varying degrees of persistence of hypertension.

Rasmussen and Boe[18] hospitalized their patients and divided them into three groups on the basis of resting blood pressure levels. The levels

TABLE VII—MORTALITY AMONG HYPERTENSIVE PATIENTS
5-10 Years After First Examination or Operation

Hypertension Group or Grade Eyegrounds	*Keith, Wagener, Barker*			*Smithwick*		
	No. Cases	*No. Deaths*	*Mortality*	*No. Cases*	*No. Deaths*	*Mortality*
1	10	4	40.0%	86	9	10.5%
2	26	17	65.3%	89	22	24.8%
3	37	34	92.0%	82	37	45.2%
4	146	145	99.3%	42	22	52.4%

selected were 90-109, 110-124, 125 and over. The mortality rates for cases falling into the three groups were determined after a period of six years had elapsed since the original examination. We have divided our 317 cases in the same fashion and the mortality rates are included for comparison in Table VI. In their series, as in ours, the mortality rate increased as the resting diastolic level increased. The rates were considerably lower in the corresponding groups treated surgically.

Mortality According to Eyeground Changes: In 1939, Keith, Wagener and Barker[22] emphasized the importance of the changes in the eyegrounds of hypertensive patients as a guide to prognosis. A series of 219 patients was divided into four groups largely on this basis. The patients who fell into group I had mild narrowing or sclerosis of the retinal arteries. Those in group II had moderate to marked sclerosis of the retinal arteries characterized especially by exaggeration of the arterial reflex and arteriovenous compression. Group III contained patients with angiospastic retinitis characterized especially by edema, cotton-wool exudate and hemorrhages in the retina superimposed upon a combination of sclerotic and spastic lesions in the arterioles. If measurable edema of the optic discs was added to this picture the case was placed in group IV. These patients were followed for a period of five to ten years at which time the mortality rates were determined and survival curves were constructed for each of the four groups. The prognosis was shown to vary for each group. They felt that their series of cases offered a good control for any specific form of therapy since treatment consisted of general measures, especially with regard to diet and rest and the regular use of certain sedatives.

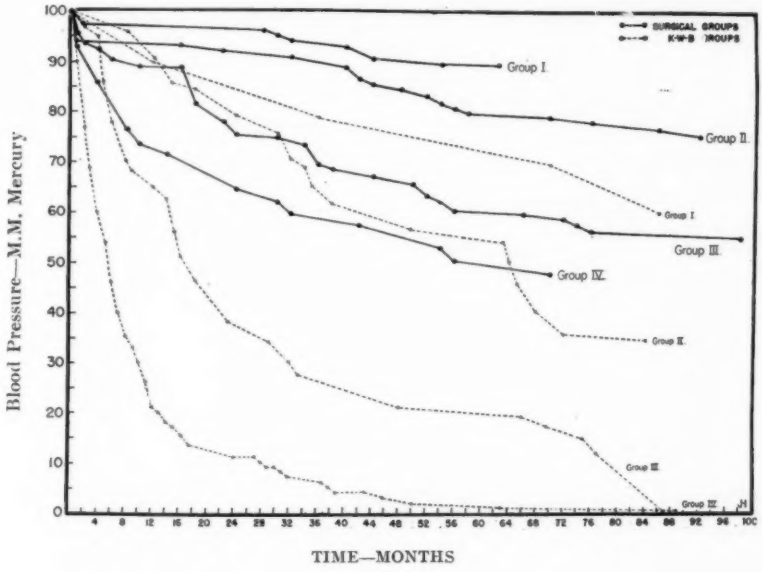


Fig. 2—In this figure the survival curves for 299 hypertensive patients treated surgically are compared with the survival curves for the Keith, Wagener and Barker series of 219 medically treated patients. Both series are divided into four groups according to Keith, Wagener and Barker criteria. The survival curves for the surgical series (heavy lines) may be compared with those of the medical series (dotted lines) group for group. It is apparent that the survival rate is much higher in the surgical series group for group. The number of patients in the medical series group 1 is too small for statistical analysis. The difference in the survival rates for medical and surgical patients in groups 2, 3 and 4 is highly significant statistically. This indicates that the life expectancy for these patients has been materially increased by surgical therapy.

Because of their observations, we have arranged our cases into four groups using their eyeground classification as the primary basis for this subdivision. Of the 317 cases in our series, 18 were considered to have normal eyegrounds. Since there were no cases of this sort in the Keith, Wagener and Barker series, we have eliminated these. The remaining 299 cases have been divided into four groups. The mortality rates for the five to ten-year period after operation are given in Table VII. The findings of Keith, Wagener and Barker are included for comparison. The mortality rates for the different groups vary in our series just as in theirs. There is, however, a marked difference between the cor-

TABLE VIII—METHOD USED FOR DETERMINING THE NUMERICAL GRADE OF HYPERTENSIVE PATIENTS

Factors To Be Considered		*Numerical Value of Each Factor*
C.V.A. without or with minor Residual Abnormal ECG Enlarged Heart Impending Failure	P.S.P. less than 25% in 15 minutes or 60% in 2 hours Age 50 or over Mild Angina	1
C.V.A. with Residual* Frank Congestive Failure Moderate Angina	P.S.P. less than 20% in 15 minutes Unsatisfactory response to sedation	2
P.S.P. less than 15% in 15 minutes		3
Nitrogen Retention		4

* Cerebral deterioration or definite involvement of arm and/or leg.

responding groups in the two series in favor of the patients who were treated surgically. There are too few group I cases in the control series for statistical analysis. The differences observed between group II, III, and IV cases are highly significant statistically. This indicates that the prognosis for many hypertensive patients has been significantly improved by surgical therapy. The same data, presented in the form of survival curves, are shown in Figure 2. This is a figure comparing 299 surgical cases with Keith, Wagener and Barker's 219 medical cases.

SELECTION OF CASES FOR SPLANCHNICECTOMY

Since this paper was presented, further control data for non-surgically treated patients have appeared in the literature. Palmer, Loofbourow and Doering[24] have given mortality rates for 430 cases treated medically and followed for an average period of 8 years. These cases were divided into four groups according to the severity of the cardiovascular changes at the beginning of treatment. Their classification differs from that of Keith, Wagener and Barker in that the degree of damage in the most affected area is the determining factor for grading, rather than the change noted in the eyegrounds. This classification is also helpful in arranging patients into more comparable groups but as

TABLE IX—TWO EXAMPLES OF THE METHOD FOR DETERMINING THE NUMERICAL GRADE OF HYPERTENSIVE PATIENTS

EXAMPLE 1			EXAMPLE 2		
Factors Considered	*Numerical Value*		*Factors Considered*	*Numerical Value*	
Abnormal ECG	1		Abnormal ECG	1	
C.V.A. without residual	1		Enlarged Heart	1	
P.S.P. 20% in 15 minutes	1		P.S.P. 10% in 15 minutes	3	
Total	3	= Numerical Grade	*Total*	5	= Numerical Grade

with the Keith, Wagener and Barker classification still permits of wide variations in the patient material in each group because so many other variables of importance are not controlled.

For this reason we have adopted a method for grouping hypertensive patients in which many variable factors are controlled. In order to decide into which of our five groups a particular patient belongs, it is first necessary to determine the numerical grade of the patient. For this purpose, many of the variable factors which have been discussed are assigned a numerical value. This plan is somewhat similar to that utilized by Hinton.[10] The numerical value for each of the factors considered is given in Table VIII. The total of the numerical values determines the numerical grade of a particular patient. Two examples of this plan for estimating the numerical grade are given in Table IX.

It was found that the mortality rate over a five to ten-year period of observation following operation was 12 per cent for patients with a numerical grade of less than 4, and 62 per cent for those with numerical grade of 4 or more. Conseqently the cases were divided into two groups according to whether the numerical grade was less than 4 or 4 or more. Patients with a numerical grade of less than four will fall into our groups 1 or 2. Those with a numerical grade of 4 or more will fall into our groups 3, 4 or 5. The other factors which determine the group for a particular case, in addition to the numerical grade, are the sex, eyegrounds, the severity of the cardiovascular changes in the cerebral, cardiac or renal areas, and the severity of the resting diastolic blood

TABLE X—CLASSIFICATION OF HYPERTENSIVE PATIENTS

Criteria for Grouping

Group	*Numerical Grade*	*Other Factors*
1	Less than 4	Females and males, eyegrounds grade 0 or 1. Females with eyegrounds grade 2 or 4.
2	Less than 4	Females with eyegrounds grade 3. Males with eyegrounds grade 2, 3, or 4.
3	4 or more	Resting diastolic level below 140 m.m. C.V.A. with residual, or frank congestive failure, or a P.S.P. below 15% in 15 minutes combined with a poor response to sedation, not present.
4	4 or more	Same as 3 except one or more of cardiovascular changes referred to are present.
5	4 or more	Resting diastolic level 140 m.m. or more.

pressure level. These are indicated by Table X. It is thus possible to place any hypertensive patient into one of our five groups and since so many variables are controlled, it should make the patient material in each group much more comparable. It should be understood that this discussion applies only to patients who have persistent hypertension as we have defined it, and does not apply to patients with so-called transient hypertension.

In Table XI, the observed mortality rates for the patients in each of our five groups are given. The estimated mortality rates for these same patients as judged by both the Keith, Wagener and Barker, and the Palmer, Loofbourow and Doering control data are also recorded for comparison. It is apparent that there is a very marked difference for group 1, 2 and 3 patients, but no difference for group 4 and 5 patients. This indicates that surgery has failed to modify the mortality rate for patients in groups 4 and 5; and I feel that this constitutes adequate reason for advising against operation in patients who fall into these two groups. On the other hand, it appears that operation has been well worthwhile for patients falling into our groups 1, 2 and 3. A more detailed discussion of this matter is in press.[25]

SUMMARY

The surgical treatment of hypertension is discussed with particular reference to operations upon the sympathetic nervous system.

TABLE XI—MORTALITY RATES FOR SURGICALLY TREATED HYPERTENSIVE PATIENTS FOLLOWED 5-10 YEARS COMPARED WITH MORTALITY RATES ESTIMATED FROM THE KEITH, WAGENER AND BARKER, AND PALMER, LOOFBOUROW AND DOERING CONTROL DATA

	Surgical Series (Smithwick) Observed Mortality			*Medical Series* Mortality Estimated From	
Group	*No. Cases*	*No. Deaths*	*Mortality*	*K.W.B. Data*	*P.L.D. Data*
1	175	13	7%	54%	47%
2	80	18	23%	86%	84%
3	52	14	27%	73%	74%
4	38	31	82%	79%	82%
5	36	33	92%	91%	83%

The favorable as well as the unfavorable effects of surgery of this type are commented upon. If too radical and inappropriate procedures are avoided, the beneficial effects will outweigh the untoward effects in the great majority of cases.

Such comparisons as can be made between surgically and non-surgically treated hypertensive patients followed for five to ten years are distinctly favorable to the surgical series.

The necessity for dividing hypertensive patients into more comparable groups, in which many of the variable factors encountered in this disorder are controlled, is emphasized.

A plan for dividing hypertensive patients into five groups is presented. The actual and estimated mortality rate for each group is given. On this basis, it appears that surgery has been well worthwhile in group 1, 2, and 3 cases. It has not affected the prognosis in group 4 and 5 cases and appears contraindicated in patients falling into these two groups.

REFERENCES

1. Smith, H. W. Hypertension and urologic disease, *Am. J. Med.*, 1948, *4*:274.
2. Adson, A. W. and Brown, G. E. Malignant hypertension: report of case treated by bilateral section of anterior spinal nerve roots from the sixth thoracic to the second lumbar, inclusive, *J.A.M.A.*, 1934, *102*:1115.
3. Craig, W. M. and Adson, A. W. Hypertension and subdiaphragmatic sympathetic denervation, *S. Clin. North America*, 1939, *19*:969.

4. Peet, M. M. Splanchnic section for hypertension; a preliminary report, *Univ. Hosp. Bull., Ann Arbor,* 1935, *1*:17; Surgical treatment of hypertension, *Proc. California Acad. Med.*, 1935-36, *5*:58; and Surgical treatment of hypertension, *J. internat. chir.*, 1940, *5*:1.
5. Smithwick, R. H. Technique for splanchnic resection for hypertension, *Surgery*, 1940, *7*:1.
6. Grimson, K. S. Total thoracic and partial to total lumbar sympathectomy and celiac ganglionectomy in treatment of hypertension, *Ann. Surg.*, 1941, *114*:753.
7. de Takats, G., Heyer, H. E. and Keeton, R. W. Surgical approach to hypertension, *J.A.M.A.*, 1942, *118*:501.
8. Poppen, J. L. Technic for supradiaphragmatic and infradiaphragmatic sympathectomy for hypertension, *Lahey Clin. Bull.*, 1943, *3*:151; correction, *ibid.*, *3*:187.
9. Ray, B. S. Conferences on therapy: surgical treatment of hypertension, *New York State J. Med.*, 1945, *45*:2515.
10. Hinton, J. W. End results of thoracolumbar sympathectomy for advanced essential hypertension, *Bull. New York Acad. Med.*, 1948, *24*:239.
11. Rowntree, L. C. and Adson, A. W. Bilateral lumbar sympathetic neurectomy in treatment of malignant hypertension: report of case, *J.A.M.A.*, 1925, *85*:959.
12. Smithwick, R. H. Surgical treatment of hypertension, *Am. J. Med.*, 1948, *4*:744.
13. Smithwick, R. H. Continued hypertension: prognosis for surgically treated patients, *Brit. M. J.*, 1948, *2*:237.
14. Wilkins, R. W., Culbertson, J. W. and Smithwick, R. H. Effects of various types of sympathectomy upon vasopressor responses in hypertensive patients, *Surg., Gynec. & Obst.*, 1948, *87*:661.
15. Stanton, J. R., Lyon, R. P., Freis, E. D. and Smithwick, R. H. Blood and "available fluid" (thiocyanate) volume studies in surgical patients; operative and postoperative blood loss with particular emphasis upon uncompensated red cell loss, *Surg., Gynec. & Obst.*, 1949, *89*:181.
16. Peet, M. M. and Isberg, E. M. Surgical treatment of essential hypertension, *J.A.M.A.*, 1946, *130*:467.
17. Canabal, E. J., Thomson, H. F. W. and White, P. D. Electrocardiogram in hypertension; electrocardiograms of hypertensive patients followed for a long time without splanchnic resection in comparison with those in patients who had had splanchnic resection, *Am. Heart J.*, 1945, *30*:180.
18. Rasmussen, H. and Bøe, J. Prognosis of essential hypertension, with remarks respecting indications for operative treatment, *Acta Med. Scandinav.*, 1945, *120*:12.
19. Isberg, E. M. and Peet, M. M. Influence of supradiaphragmatic splanchnicectomy on the heart in hypertension, *Am. Heart J.*, 1948, *35*:567.
20. Janeway, T. C. Clinical study of hypertensive cardiovascular disease, *Arch. Int. Med.*, 1913, *12*:755.
21. Blackford, J. M., Bowers, J. M. and Baker, J. W. Follow-up study of hypertension, *J.A.M.A.*, 1930, *94*:328.
22. Keith, N. M., Wagener, H. P. and Barker, N. W. Some different types of essential hypertension: their course and prognosis, *Am. J. M. Sc.*, 1939, *197*: 332.
23. Bechgaard, P. Arterial hypertension: follow-up study of 1000 hypertonics, *Acta. Med. Scandinav.*, 1946, supp. *172*.
24. Palmer, R. S., Loofbourow, D. and Doering, C. R. Prognosis in essential hypertension: eight-year follow-up study of 430 patients on conventional medical treatment, *New England J. Med.*, 1948, *239*:990.
25. Smithwick, R. H. Surgical physiology of hypertension, *S. Clin. North America, in press.*

RECENT ADVANCES IN THE THERAPY OF THE MORE COMMON PROTOZOAN AND HELMINTHIC INFECTIONS OF MAN*

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INTRODUCTION

IN DISCUSSING recent advances in the treatment of parasitic infections, one must not overlook the fact that specific agents for the therapy of some of these infections antedate by centuries so called modern chemotherapy. The story of quinine is well known and needs no comment. Male fern was known to Pliny and Galen, and was used extensively in Europe in the 18th century against tapeworms. The essential oils were used as anthelminthics by the American Indians in the days of Columbus, and specifically against hookworm in Europe in 1881. Screening techniques now used in the search for therapeutic agents against infections were first systematically explored in the experimental chemotherapy of parasitic diseases. As a result important contributions were made in the treatment of animal and human parasitic infections. In addition, the extension and application of some of these agents in the treatment of non-parasitic diseases have given us in more recent times extremely useful drugs, of which salvarsan and the sulfonamides are perhaps the most notable examples.

During the recent war we had to maintain our men in good health in tropical areas in spite of potentially great risks of infection and morbidity from parasitic infections. This necessitated re-evaluation of existing therapeutic agents as well as stimulated the systematic search for new, possibly more efficient drugs and better schedules of treatment.

In my discussion tonight I will review the present status of the therapy of such parasitic infections which ordinarily occur in this country, or, which by virtue of their introduction in a significant number of veterans, may constitute a small segment of the patient population.

* Presented at the Graduate Fortnight, The New York Academy of Medicine, October 15, 1948.

Infections Caused By Pathogenic Protozoa

From the standpoint of total numbers, potential disability, or the likelihood of their occurrence in medical practice in the United States, the infections caused by the plasmodia and *Endamoeba histolytica* are the most important ones produced by protozoa. Consequently discussion of the latter will be limited to the treatment of malaria and amebiasis.

MALARIA

This disease occurs normally in the United States, and in addition one should note that more than a half million hospital admissions during World War II were attributable to malaria. The progress in the treatment of this infection will be reviewed briefly by consideration of the following: (a) The pharmacology of antimalarial drugs. (b) Quinine versus atabrine. (c) 4-amino quinoline drugs with special reference to chloroquine. (d) 8-amino quinoline drugs and the cure of vivax malaria.

(a) *The pharmacology of antimalarial drugs:* Prior to the war the use of antimalarial drugs with regard to dosage and treatment schedules was largely empiric. Commonly employed treatment regimes were the result of clinical trials in patients in various parts of the world, and were rarely the same in any two places. It was obvious that in order to have a baseline for evaluating various agents to be tested in a large scale screening program, standardized infections with known strains, and arbitrarily defined treatment response, would have to be investigated. These studies were largely initiated by Shannon[1] and his group, and rapid progress was made possible by the discovery of relatively simple accurate chemical methods for determining antimalarial drugs in blood and tissues. As a result, one could study the absorption, storage, disposition and excretion of numerous potentially valuable drugs. And, in conjunction with the determination of antimalarial activity in animals and man, it was feasible to work out the optimum treatment or suppressive schedule for the best drugs.

Table I and Figure 1 were furnished by Dr. David P. Earle, Jr., and were prepared from data published by Shannon[1] and his colleagues.* Figure 1 notes the correlation between plasma level and therapeutic effect and the definition of the so-called minimum effective level of

* Reproduced from the Harvey Lectures, 1945-1946 by permission of The Harvey Society.

TABLE I—THE RELATIONSHIP BETWEEN TOTAL DOSAGE, THE MEAN PLASMA CONCENTRATION (FOR 4 DAYS) OF QUINACRINE AND ITS THERAPEUTIC EFFECT IN THE STANDARD BLOOD-INDUCED THERAPEUTIC TRIAL WITH McCOY VIVAX MALARIA

Total dosage is given rather than priming and daily dosage because of the characteristics of its physiological disposition

Patient	*Total dosage*	*Plasma quinacrine, 4-day mean*	*Therapeutic result*		
			Class I	*Class II*	*Class III*
	g.	*mg./l.*			
Tra	0.7	44			+
Wal	0.7	39			+
Bel	0.7	34			+
Cra	0.7	32			+
Cha	0.7	31			+
Dar	0.85	27			+
Woi	0.7	26			+
Wor	0.7	26			+
Qui	0.7	26		+	
Cas	0.55	25			+
Dav	0.45	24		+	
Far	0.45	23		+	
Hau	0.6	22		+	
Mis	0.6	21			+
She	0.45	21		+	
Eic	0.45	21		+	
Mar	0.35	19		+	
Chi	0.45	19		+	
Lor	0.70	19		+	
Kas	0.60	18		+	
Sch	0.70	18		+	
Ami	0.45	16		+	
Ash	0.75	16		+	
Ger	0.55	16		+	
Coo	0.35	15		+	
Bit	0.35	13		+	
Dem	0.35	13		+	
Sca	0.45	12		+	
Cuo	0.35	10		+	
McB	0.45	8	+		
Sau	0.25	6	+		
Cra	0.25	6	+		
Kel	0.25	3	+		

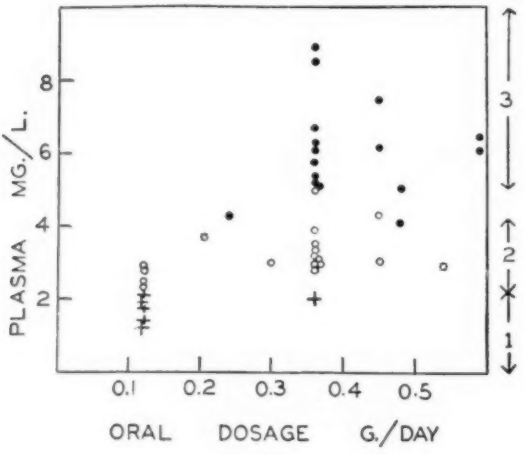

Fig. 1

above 4 mg./L. for quinine, and 30 micrograms/L. for atabrine in a given strain of vivax malaria. From this type of observation and a knowledge of the disposition and excretion of the drugs it became possible by suitable initial and subsequent doses to establish and maintain effective levels for adequate termination of clinical activity.

(b) *Quinine versus atabrine:* It can readily be appreciated that a drug of such historic and established value with world-wide acceptance as quinine would be difficult to displace from the number one position in the treatment of malaria. When atabrine was introduced in 1931, the recommended dose in treatment of acute attacks was 0.1 gram three times daily for 5 days. It was soon found that in many patients fever, symptoms and parasitemia were not promptly controlled with that schedule. As a result there were numerous revisions in dose, and the feeling in many areas was that if atabrine was to be used at all, it should be preceded by several days of quinine therapy for control of the early acute signs and symptoms of the attack. However, when the pharmacology of atabrine was investigated, as indicated, the reason for the relatively poor immediate effect was apparent: The initial small doses were found to be localized in the tissues leaving little in the plasma to exert a chemotherapeutic effect. Ultimately, with continued administra-

tion even on small initial doses, plasma levels are achieved and a satisfactory clinical result is obtained. However, with sufficiently large initial doses an effective level could be created during the first day of treatment, and this level maintained by the serial administration of small doses thereafter. Thus, 1 gram given in divided doses during the first 24 hours, followed by 0.3 gram daily for the next 6 days, provided average daily levels of 41 to 52 micrograms per liter from the second to the eighth day of treatment, and significantly higher levels during the first 24 hours. It had previously been determined by Shannon[1] that with maintained levels of 30 to 40 micrograms per liter vivax infections are promptly controlled. Thus a rational basis for the optimum use of atabrine resulted in the 2.8 Gm. in 7 days schedule we all now know. The clinical effectiveness of this schedule and its superiority over quinine from the standpoint of control of fever, parasitemia, and interval to relapse are summarized from studies by Most and Hayman.[2] Within 12 hours after the first dose of atabrine some patients already had negative smears, and by 96 hours virtually all were clear. With quinine on the other hand, only 7 per cent were parasite free at 24 hours, and almost a fourth still had parasites at 96 hours. In a few patients parasites persisted for 132 hours. There is little question of the more rapid action of atabrine in clearing the blood of parasites. The contention that quinine controlled fever more quickly than atabrine was not borne out in these studies. It was found that atabrine and quinine were equally effective in relapses; about 10 per cent in each group having fever 24 hours after treatment was begun. But atabrine was superior in primary attacks since only 16 per cent had fever on the second day after its use compared to 32 per cent with fever after quinine.

Since neither quinine nor atabrine are curative drugs, the question of the interval to relapse following treatment, is perhaps of greater importance than initial control of fever and parasitemia. In the case of quinine relapses begin as soon as 10 days after treatment, whereas after atabrine only a few occur in less than 30 days. In large groups of patients studied with Pacific and Mediterranean vivax infections the mean interval to relapse after quinine was 22 days and after atabrine 50 days. Thus, atabrine affords a significantly longer symptom-free interval than quinine, and largely does away with extremely short term relapses.

(c) *4-Amino Quinolines:* The drug of this series which to date has had the most extensive basic and clinical study is chloroquine. Chloro-

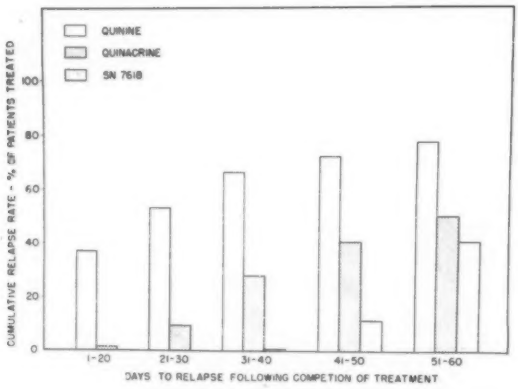

Fig. 2—Interval to relapse following therapy with quinine, atabrine and chloroquine

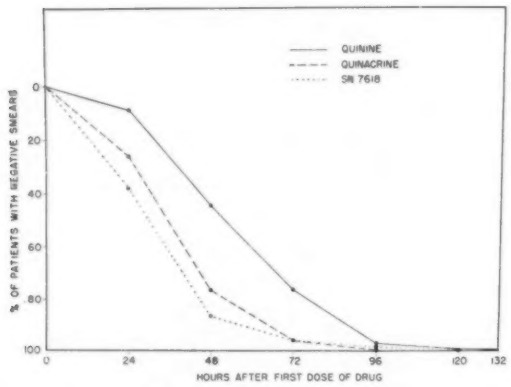

Fig. 3—Effect on parasitemia with quinine, atabrine and chloroquine

quine behaves pharmacologically very much like atabrine except it persists longer in the body. Also from the standpoint of its antimalarial activity, effective levels in the plasma are in the range of 10 gammas per liter, and are achieved with relatively small doses by mouth. As a result of both these properties it is possible to maintain effective suppression by single weekly doses of the drug and to accomplish satisfactory termination of attacks by treatment schedules of from 1 to 4 days.

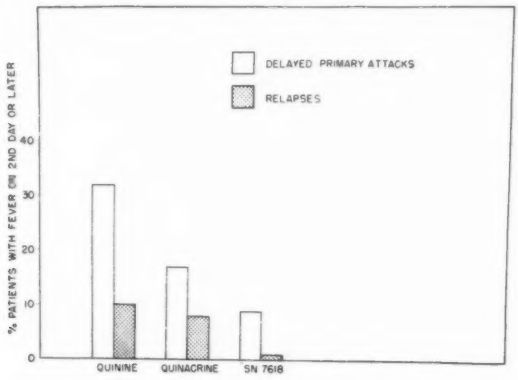

Fig. 4—Control of fever during treatment with quinine, atabrine and chloroquine

Both from the standpoint of short term treatment and suppression it is decidedly less toxic than either atabrine or quinine. Prolonged use does not produce the yellow skin color atabrine does, nor does it produce symptoms of cinchonism. Its effectiveness in controlling parasitemia and fever, and in providing a longer interval before relapse is demonstrated in Figures 2, 3 and 4 in which chloroquine is compared to quinine and atabrine in these respects. The data are from studies by Most and his colleagues[3] conducted during the war.

With respect to control of parasitemia, one notes 86 per cent of patients were cleared of parasites by 48 hours and practically all were free by 96 hours. Thus, during the first 48 hours chloroquine is definitely more active than either quinine or atabrine, and after that both are better than quinine. Chloroquine also controlled fever more promptly than quinine or atabrine in primary attacks, regardless of initial parasite density or geographic origin of the infection. Only 2 per cent of patients on chloroquine had fever 24 hours after treatment was begun compared to about 10 per cent for both quinine and atabrine.

With regard to the interval to relapse after treatment, only 1 per cent of chloroquine treated patients had another attack within 40 days after treatment, whereas 67 per cent and 28 per cent relapsed after quinine and atabrine respectively. Thus, short term relapses are virtually abolished with chloroquine. Following its use, only one-sixth of the

relapses which would occur in 4 months took place within the first 2 months after treatment, providing a mean interval to relapse of 61 days compared to 22 and 50 days respectively for quinine and atabrine.

Finally the ease of administration of chloroquine in treatment schedules of 1.0 gram of base in 1 day or 1.5 grams in 3 or 4 days, as well as freedom from noteworthy toxicity, make this drug a most attractive one for suppression and treatment of acute attacks of vivax malaria. Despite the convincing evidence which has been published in behalf of chloroquine many clinicians prefer quinine. The responsibility for poor suppression, toxicity, and short intervals to relapse is theirs. However, the effectiveness of chloroquine for suppression and treatment of various strains of vivax and falciparum malaria in various parts of the world as well as its value by mouth or parenterally in fulminating falciparum infections remains to be determined.

(d) *8-Amino Quinolines and the Cure of Vivax Malaria:* Unfortunately clinical studies with these drugs were not commenced until late in the war. If some of the relatively safe 8-amino quinolines now available had been on hand earlier, we could have been spared the tremendous number of hospitalizations because of vivax malaria. Long before the war it had been shown in India that quinine and plasmochin given concurrently favorably reduced the relapse rate in vivax malaria. However, plasmochin was considered by many too toxic for extensive routine application for the required period of therapy. In military hospitals in this country the use of plasmochin for 3 to 5 days after quinine or atabrine for acute attacks of malaria, did not result in a reduction in subsequent relapse rates. Following the demonstration of the curative properties of combined quinine-plasmochin therapy in volunteers with mosquito induced vivax infections in the United States, a clinical study at Moore General Hospital in this country was undertaken and reported by Most[4] and his colleagues in November 1946. Originally 72 patients were treated and observed for more than 6 months, but since then approximately 100 patients have been treated and adequately followed. Clinical relapses occurred in only 4 per cent of treated patients compared to relapses of 80 and 90 per cent for similar groups treated with quinine, atabrine, chloroquine or other drugs. Except for abdominal cramps in most patients and methemoglobinemia or mild anemia and significant leukopenia in a small number of patients, no serious toxic reactions occurred. Treatment was completed in all cases. Each dose

of quinine was 0.6 Gm. and each dose of plasmochin was 0.02 Gm. of the naphtholate. Both drugs were given together at 8 hour intervals for 14 days. Although this dose of plasmochin does not cure a high proportion of heavy experimental infections, our dose was nevertheless curative possibly because of modification of the infection by prior suppression with atabrine. It should also be emphasized that the patients were in good physical condition, were hospitalized during treatment, and were all white. This is noted since the incidence of severe hemolytic reactions from plasmochin is more common in negroes and other pigmented races.

More recently, 8-amino quinolines, which in experimental human infections are more active and less toxic than plasmochin, have been introduced. Of these pentaquine and isopentaquine have been most intensively studied by Alving[5] and his colleagues. More than 500 veterans with relapsing vivax malaria have been treated with 10 mg. of pentaquine base and quinine at 8 hour intervals for 14 days. In New York Straus and Gennis[6] had only one failure in 50 patients so treated and adequately followed afterwards. Coggeshall[7] in Chicago has treated about 400 men with combined pentaquine-quinine on an out-patient basis. There can be little question that these drugs are curative and represent a major advance in the cure of vivax infections. Thus, as a result of the wartime necessity and interest in malaria, it is now possible to effectively suppress, treat, and cure malaria.

Amebiasis

The average incidence of infection with *E. histolytica* in the United States has been widely published as being in the range of 10 per cent of the population, with variations from 1 to 40 per cent or more for various parts of the country. Stool surveys conducted at military separation centers and military hospitals in the United States indicated that probably 5 to 15 per cent of veterans who served in the Pacific Theaters are infected with this parasite. In this city Shookhoff[8] has reported an infection rate of about 10 per cent in Pacific veterans. The speaker has found 8 per cent of veterans from various Philippine Islands carrying *Endamoeba histolytica*. Study of a cross section of veterans in the city in various clinics and hospitals without consideration of geographic areas of service or symptoms indicates that probably not more than 4 per cent have amebiasis. It is apparent, then, that from the standpoint

of treatment, amebiasis is an important infection, even if one overlooks the clinical and epidemiologic implications.

The number and diversity of drugs available for the treatment of amebiasis. and the need in many cases, of parenteral, oral and/or intra-rectal therapy, as well as prolonged treatment with more than one drug, is ample evidence of the desirability of having more effective amebicidal agents than are now at hand. In the following Table are listed the more important standard drugs used in the treatment of amebiasis as well as several recently introduced agents. I shall briefly review the present status of these drugs.

TABLE II—DRUGS USED IN TREATMENT OF AMEBIASIS

(a) EMETINE
(b) IODO-QUINOLINES
1. Chiniofon
2. Diodoquin
(c) METALS
1. Carbarsone
2. Thioarsenites
3. Wia
(d) 4-AMINO QUINOLINES
1. Chloroquine
(e) ANTIBIOTICS
1. Para-amino-benzoic Acid
2. Bacitracin
3. Aureomycin

(a) EMETINE:

This drug has been the stand-by for a long time in the treatment of clinically severe amebic colitis, and amebic hepatitis or abscess, as well as other forms of extra-colonic amebiasis. Satisfactory, often dramatic results are well known from the use of emetine. However, potential toxicity from prolonged or exaggerated use, a high failure or relapse rate in cases in which it alone is used, and apparent resistance of some severe recurrent or chronic cases leave much to be desired from emetine as a universal amebicide. At the present time emetine is used in daily doses of 0.06 Gm. for from 4 to 7 days in clinically severe or moderately severe amebic colitis, and from 7 to 10 days in amebic hepatitis or abscess, granuloma of the colon, pulmonary, brain or skin involvement. A similar course may be given after the lapse of 10 days, but some thought should be given to possibly severe toxic reactions before a third course is given. In this connection it might be of interest to point

out that during the war, emetine was extensively used in the American military forces, often at the dispensary level, in men who carried out their usual duties including aircraft operation. Yet, as far as I know, not a single death from emetine was reported during World War II. One should not encourage the indiscriminate use of emetine, but I think that many of the serious reactions described have resulted from large doses, prolonged therapy, intravenous use, severe chronic debilitation or other serious underlying constitutional disorders.

(b) IODO-QUINOLINES:

This class of compounds, of which chiniofon and diodoquin are but two, have gained widespread acceptance in the treatment of amebiasis. Until recently the basis of their activity has been attributed by many to their iodine content. Thus diodoquin has been said to be more effective than chiniofon, because it contained twice the iodine content of the latter, and yet, daily dosages for both are about the same, or greater, in the case of diodoquin. Diodoquin does not produce the diarrhea which frequently accompanies chiniofon therapy, and for that reason is preferred by many clinicians. In a few instances iodism has been observed in the course of prolonged diodoquin medication. Currently total daily doses of 3 grams by mouth for 20 to 30 days are advocated, and longer treatment, or several courses may be necessary in some cases, particularly those with granulomas. In clinically severe amebiasis with extensive or slowly healing ulcers, or well-established cecal deformities or granulomas, retention enemas of chiniofon are considered by some individuals a valuable adjunct to simultaneous oral iodoquinoline and parenteral emetine therapy; 200 to 700 cc. of a 2½ per cent suspension are given in one or more courses of 7-10 days each. Although cure rates from these drugs are said to be 80 to 95 per cent, critical prolonged follow-up studies in large groups of patients with infections acquired in widely scattered geographic areas are not available. As a matter of fact, whether or not it represents lack of confidence in one or all the drugs one cannot say, but the vogue in the treatment of amebiasis in many parts of the world and in this country is to use all available drugs, some simultaneously, and others serially and in rotation for several courses. In this way one hopes to overcome the shortcomings of any one agent and to produce a cure without the need for further study of the patient's stools.

(c) METALS:

1. *Carbarsone* like diodoquin and chiniofon has had widespread acceptance in many parts of the world as a suitable amebicide. Although cure rates for this drug are considered to be approximately those of the iodoquinolines, the limitations of prolonged observation of large groups of patients mentioned for the latter are applicable to carbarsone. The original dosage schedule for intestinal infections, namely 0.25 Gm. twice daily for 10 days, is adhered to by most clinicians who use carbarsone before or after one of the iodo-quinolines. With regard to the toxicity of carbarsone and the reluctance of many physicians to use this drug if hepatitis is suspected, it can be pointed out that in subjects studied at the National Naval Medical Center, no evidence of hepatic or kidney dysfunction was observed with daily doses 5 times greater than the standard dose. During the war and since we have used daily doses of 1.0 Gm. without toxicity. It is possible that increased doses of carbarsone may significantly increase its efficiency. But here again there is need for a critical re-evaluation of these agents.

2. *Thioarsenites:* For some time Hamilton Anderson and his colleagues have been studying various arsenicals in the treatment of amebiasis. Recently they have found a group of thioarsenites which they feel to be superior to carbarsone on the basis of monkey and human observations in this country and in Costa Rica. Of 40 patients treated, all but 2 were reported free of infection. The total number of patients treated and adequately followed is still not sufficiently great to recommend these drugs, nor has the question of toxicity, especially gastrointestinal, been completely worked out.

3. *Wia:* This drug containing both bismuth and arsenic in organic form was first reported on by Hauer[9] in 1943. Wia alone or in combination with chiniofon when tested in German troops of the Afrika Korps was said to eliminate cysts from the stool promptly, but was not satisfactory in acute virulent infections. More recently Berberian[10] reported cure of 24 out of 25 patients treated with Wia alone compared to 5 of 11 treated with chiniofon, and 33 of 38 were cured after treatment with Wia and chiniofon combined or alternated. No side effects are reported. Whether or not this drug will have an important position in the therapy of amebiasis one cannot say at this time, but preliminary observations in this city with daily doses of 1.5 Gm. for 7 days are encouraging.

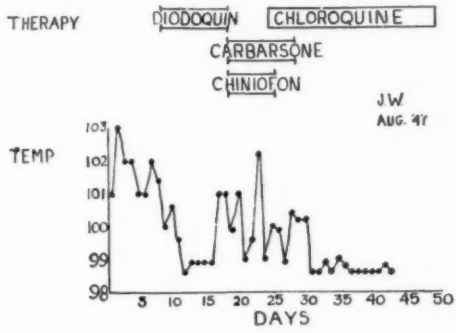

Fig. 5—Temperature chart in case II treated with chloroquine

(d) 4-AMINO QUINOLINES:

Chloroquine: Conan[11] demonstrated that chloroquine has a moderate degree of amebicidal activity in intestinal infections. In a series of 32 patients treated with 0.3 gram of base for 21 days and adequately followed after treatment, cures were effected in 50 per cent of the patients. This is an important observation not necessarily in relation to the use of chloroquine in colonic amebiasis, but rather in relation to the fact that the basis of activity of the so-called organic iodides may be the quinoline nucleus, and if this is so, a new group of compounds is available for investigation. In this connection, a recently developed technique of infecting young rats by intracecal inoculation of cultures of amebae represents an important advance in the experimental chemotherapy of amebiasis. Large scale screening tests in industrial and university laboratories now in progress may provide us with agents which are universally active in all forms of amebiasis, and which otherwise may have been discarded because of poor *in vitro* activity.

In addition to the amebicidal activity of chloroquine in some cases of intestinal amebiasis, Conan[12] also has demonstrated chloroquine to have a very high degree of activity in acute amebic hepatitis and abscess. In one of these patients emetine had failed to control the infection. Others have observed equally good results with chloroquine in hepatitis. Figures 5 and 6 are illustrative of the response to chloroquine in 2 patients. The first case was presented by Murgatroyd and Fairley[13]

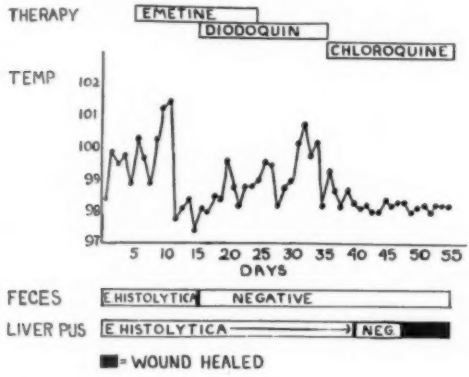

Fig. 6—Murgatroyd and Fairley's case treated with chloroquine

in London, and the data for the slide were sent to Dr. Conan who prepared it. The patient had an amebic abscess of the liver and was drained 4 months previously. He did not respond to emetine parenterally, by mouth or irrigation of the abscess cavity, although emetine and diodoquin cleared his intestinal tract of amebae. He received 0.75 Gm. chloroquine by mouth for 18 days. Within 4 days the liver pus contained no amebae, and within 12 days the wound was healed. Fever was controlled promptly.

The second case was treated at the Veterans Hospital, New York. The patient had a large tender liver, fever, leukocytosis, amebae in the stools, and a positive complement fixative for amebiasis. He was given 0.6 Gm. chloroquine by mouth for 2 days, and 0.3 Gm. daily for the next 19 days. The response was prompt and recovery complete. If these results are borne out in larger groups of patients in various parts of the world, and if one appreciates the ease of oral medication with chloroquine, and the freedom from significant toxicity, then this finding may represent a noteworthy contribution to the treatment of amebiasis.

(c) ANTIBIOTICS:

1. *Para-amino-benzoic acid:* Dwork[14] (1948) reported apparent cure of 4 of 9 patients with intestinal amebiasis treated with para-amino-

benzoic acid. The frequency and the size of each dose as well as the relatively poor cure rate observed would preclude its general use in the treatment of amebiasis. However, the fact that para-amino-benzoic acid possesses some activity is important from the standpoint of the possible antibiotic mode of action of other agents unrelated to those now in use.

2. *Bacitracin:* The background for the use of bacitracin in the treatment of amebiasis is of interest. For a long time many investigators have attempted to culture *Endamoeba histolytica* free of bacteria. Although the solution has not been resolved, some progress has been made with heat killed filtrates and dead bacteria, along with the use of penicillin and streptomycin in cultures. In order to determine whether bacitracin might help eliminate or reduce the bacteria in the amebae cultures it was studied in E. C. Faust's[15] laboratory at Tulane and found to inhibit or kill the amebae to a greater degree than the accompanying bacteria. Alfred Longacre,[16] Louisiana State University, then treated patients with amebic colitis using bacitracin in divided doses orally. He noted excellent clinical response with disappearance of amebae from the stools and rapid healing of ulcers in some patients. In this city, Most, Grossman, Miller and Conan[17] have confirmed the observations of Longacre in both acute clinical cases and in non-symptomatic carriers. Currently total daily doses by mouth of 40 to 160,000 units for 10 to 20 days are being studied, but it is possible optimum treatment may require greater doses for more than 20 days in some cases. Apparently bacitracin is not absorbed, and no significant toxicity or symptoms have been noted from its oral use. We have treated more than 50 patients to date, and cure rates of 60 to 80 per cent are probable on the basis of mean observation periods of 6 months after therapy. In severe dysentery, clinical response may be dramatic in a few days with cessation of diarrhea, healing of ulcerations and disappearance of *E. histolytica.* It is of great interest that in some such cases the amebae reappear in the stools days to months after therapy has been completed, but the patient has no demonstrable lesions and is symptom-free. Bacitracin is known to result in disappearance of gram-positive organisms and anaerobes from the stools. It may be that the initial lesions are produced by *E. histolytica*, but are enlarged to clinical significance by these bacteria; or the bacteria furnish essential metabolites for the growth or virulence of *E. histolytica.* In either case bacitracin

apparently influences the bacterial parasite relation in the colon to the benefit of the patient in a significant number of instances.

3. *Aureomycin:* More recently we have treated patients with amebiasis with 20 Gm. of aureomycin given by mouth during 10 days. To date, of 8 patients so treated 7 have remained free of *E. histolytica* following therapy.

Helminths

In general with several notable exceptions the status of the therapy of the common helminths is satisfactory. Advances are represented by the introduction of new drugs or the revision of treatment schedules or techniques with drugs of established value. My remarks will be limited to the status of the therapy of the worms most often encountered by the practitioners in this country.

THE NEMATODES OR ROUNDWORMS

Of the more common roundworms, the treatment of Ascaris with hexylresorcinol and *Enterobius*, or pinworm, with gentian violet is on the whole satisfactory, although a drug less toxic and given for a shorter time than gentian violet would be desirable against the pinworm. Tetrachlorethylene has been considered the drug of choice in the treatment of hookworm infections. However, during and after the war it was noted that many patients were still passing hookworm eggs in the stools, in spite of having had during a period of months, from one to twelve treatments with tetrachlorethylene. Most and Hayman[18] reported that almost all the adult worms recovered from such patients were *Ancylostoma duodenale* rather than *Necator americanus*, the hookworm of this country. In the same study it was found that only 25 per cent of patients treated for the first time for hookworm and found to have *Ancylostoma* infections were cured by a single course of 3 to 5 cc. of tetrachlorethylene. These patients were almost exclusively from various Pacific Islands. In contrast to this poor result similar doses of tetrachlorethylene cured more than three-fourths of *Necator* infections. Since the vast majority of hookworm infections were light and did not represent hookworm disease, the difficulty in the elimination of *Ancylostoma* in patients in this country is not serious. One should consider the areas of exposure if results of treatment are poor, and also in well sanitated areas the actual need for re-treatment is negligible. Certainly

the potential risks from carbon tetrachloride and oil of chenopodium in full doses, although these drugs may be more effective against *Ancylostoma,* do not warrant their use in this country. However, the persistence of *Ancylostoma* in spite of tetrachlorethylene therapy raises the possibility of its introduction into the southern United States.

Strongyloides and *Trichurus* infections which are relatively common in some parts of the United States, and particularly *Trichurus* in Pacific veterans, deserve comment. In the case of *Strongyloides,* treatment with 3 daily doses of 60 mg. each of gentian violet for 16 days is the standard textbook recommendation. However, if patients are followed carefully, it will be found that in a large number larvae reappear in the stools within several months after treatment. It should also be known that the commonly used preparation of gentian violet is designed to disintegrate 4 hours after ingestion, but the adult worms we seek to kill are high in the small intestine. D'Antoni[19] originally advocated larger doses of gentian violet. We have found increasing each dose by one pill each day until the maximum number tolerated, usually 12 to 16 per day, are taken for about 2 weeks, produces a satisfactory result in a high proportion of cases treated. In the case of *Trichurus* which rarely produces, in this country at least, disease or symptoms, treatment is unsatisfactory. In areas where fresh leche de higueron, the latex of several species of fig tree, is available it is used with moderately good results in eliminating the infection. Recently[20] in this country enteric tablets of emetine hydrochloride have been used experimentally with excellent results in eliminating *Trichurus* adults from the large bowel. However, in some patients dislodgment of the anterior portions of the worm brings with it a bit of mucosa in which it is embedded and bloody diarrhea may result. The preparation of emetine used is not commercially available, and further study of efficacy and toxicity would appear necessary before it could be recommended against a relatively harmless parasite. Ferric ammonium citrate, 50 per cent solution, in oral doses of 12 cc. daily has been reported to reduce egg counts 80 to 90 per cent, but actual cure rates are not known. The author has treated several cases but observed no cures, although during therapy the egg counts were markedly reduced.

Unfortunately no specific drugs are available for the treatment of trichinosis. Hetrazan, which will be discussed shortly in relation to its use in the treatment of filariasis, has not given conclusive results in a

sufficiently large number of cases of acute trichinosis to permit its evaluation at this time.

Filariasis, while no longer a problem in the United States, is of interest to us because of its prevalence in the Virgin Islands and Puerto Rico and as a result of the war its occurrence in several thousand members of our military forces. Fortunately almost all the latter infections were not severe, and are no longer clinically or otherwise detectable. Whether later on any of these men may develop elephantiasis or other sequelae of filariasis no one can say, but certainly there is no indication for any treatment except perhaps in some case reassurance. Nevertheless, a tremendous amount of effort was devoted to the investigation of possible filaricidal drugs. The number studied and results have been voluminously published, and will not be reviewed here. Various antimony and arsenic preparations were found effective in destroying the adult worms in the cotton rat, and in producing disappearance or reduction of microfilariae from the blood of man within 6 to 12 months after treatment. Neostibosan is perhaps the most effective and least toxic of these metallic agents. Undoubtedly the reduction in the total number of circulating microfilariae available to transmitting arthropods, in conjunction with antimosquito measures is important from the standpoint of the control of filariasis. More recently, Santiago-Stevenson, Oliver-Gonzalez and Hewitt[21] reported the use of "Hetrazan" (diethyl carbamyl piperazine) in Puerto Rico in 26 patients demonstrated to have microfilariae in the peripheral blood. The daily doses ranged from 0.5 to 2.0 mg./kg. administered for from 3 to 22 days. Microfilariae disappeared completely or were markedly reduced in all patients within a few days, and in 4 patients nodular tender swellings with lymphadenitis of spermatic cord or extremities suggested accompanying deaths of adult worms. No significant toxic manifestations attributable to the drug were observed. In the treatment of another form of filariasis, namely onchocerciasis in which the adult filaria worms are in subcutaneous nodules, severe local and systemic reactions even from very small doses of Hetrazan have been reported. These are presumably due to gross rapid destruction of numerous adult worms and liberation of foreign protein. Certainly the use of neostibosan and Hetrazan in the treatment of filariasis are notable chemotherapeutic contributions, but their exact place in the clinical therapy of various forms of filariasis is not yet defined.

CESTODES OR TAPEWORMS

I shall concern myself only with the beef tapeworm, *Taenia saginata*, since it is the most commonly encountered tapeworm in private practice in this part of the country and because its elimination is often not accomplished with ease. Until recently, oleoresin of aspidium has been considered the drug of choice in the treatment of all the intestinal tapeworms of man. In my experience most treatment failures are due to the use of other drugs of less efficiency, or to the use of inadequate amounts of oleoresin of questionable potency administered in capsules. If 8 grams of fresh oleoresin of aspidium is introduced into the duodenum by tube together with 30 to 45 grams of sodium sulfate and about 100 cc. of water, the probability of cure is at least 90 per cent. Preliminary purgation and a low residue diet for 24 hours previously and treatment in the fasting state facilitate recovery of the head if it is passed. Even if the head is not found, there is no need for re-treatment before 6 to 12 weeks, or until segments are again noted in the stools. In some patients the head is passed after treatment but not found, and cure is determined by a suitable period of post-treatment observation. I have not noted any significant toxicity from 8 to 12 grams of oleoresin of aspidium given as described in more than 50 patients.

Shortly before the war following Culbertson's[22] report of the beneficial effects of atabrine in a tapeworm infection of mice, I treated 4 patients with tapeworms with 0.6 to 1.0 Gm. of atabrine administered in solution intraduodenally. In one patient a brightly stained yellow complete worm was recovered. In another case an unstained worm without the head was passed, but follow-up of the patient for 4 months suggested probable cure. The other 2 patients who received 0.6 and 1.0 Gm. respectively were definite failures. During this year, Brown[23] in a review of anthelminthic therapy reported cures in all of 8 patients with tapeworms treated by Shookhoff with 0.8 or 0.9 gram of atabrine given in divided doses by mouth. Failures resulted from treatment of 3 children presumably because of vomiting. I know of 7 definite cures of 13 other patients treated with atabrine by mouth or intraduodenally, although the actual cure rate may be higher since the outcome in the remaining patients is unknown. In the same review Santiago-Stevenson is said to have noted excellent results in a small number of patients treated with 1.0 Gm. of crystalline hexylresorcinol administered intraduodenally. If this observation is confirmed and cure rates of 90 per

cent or more are reported, such treatment would be a distinct advantage because of the availability and stability of hexylresorcinol compared to oleoresin of aspidium. At the present time I think that the latter drug is the most reliable agent against tapeworms. Atabrine is simple to give if vomiting doesn't occur, but single doses of 0.8 to 0.9 gram may produce other undesirable toxic reactions. Its further trial is indicated.

THE TREMATODES OR FLUKES

The schistosomes, principally *S. mansoni* and *S. japonicum*, are the flukes which should interest us; the former because of the significant incidence of infection in Puerto Rican residents in this country, and the latter because of our military experience in the Philippines during the war. With regard to schistosomiasis japonica, one must note that approximately 1500 men contracted the infection on Leyte, and were hospitalized both abroad and in this country for study and treatment. Probably an equal, if not greater number also were infected but not recognized because of the mild original manifestations of the infection. The third group of infections occurred amongst 2000 or more American military prisoners of the Japanese interned in prison camps at Davao and elsewhere in the Philippines. The extent to which these men were infected is unknown, but a preliminary random sampling by examination of one to three stool specimens indicates the percentage to be very high.

The principal drugs used before the war in the treatment of schistosomiasis were trivalent antimony preparations, fuadin and tartar emetic. Fuadin, named after King Fuad of Egypt, was introduced by the Germans for the treatment of vesical schistosomiasis due to *S. haematobium*. The original dosage schedule of 40 cc. as a course of treatment seemed satisfactory in Egypt, though the problem of reinfection and short term observations of patients did not permit exact evaluation of its efficiency. In *S. mansoni* infections 40 cc. possibly cured more than 50 per cent of patients, and later better controlled observations indicated that 70 cc. probably cured more than 75 per cent of patients. During the war the effect of fuadin on *S. japonicum* infections was not known. The majority of our patients received overseas one or more courses of 40 cc. of fuadin. Yet we found that following treatment of cases passing viable eggs on arrival in this country with 70 cc. of fuadin the failure rate was 80 per cent. Increasing the total amount to 100 cc. but adhering to the

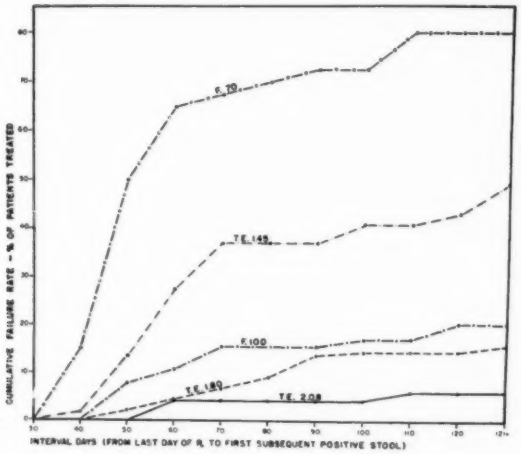
CUMULATIVE FAILURE RATE - % OF PATIENTS TREATED
INTERVAL DAYS (FROM LAST DAY OF R, TO FIRST SUBSEQUENT POSITIVE STOOL)
F. 70
TE. 145
F. 100
TE. 189
TE. 208

Fig. 7—Results of treatment of schistosomiasis japonica with fuadin and tartar emetic

alternate day schedule of 5 cc. per injection did not lower the failures materially. However. by giving 8 cc. daily until 100 cc. of fuadin had been injected the failure rates were sharply reduced. With equivalent amounts of antimony in tartar emetic the results were better on all treatment schedules as shown in the accompanying Figure 7. Thus with 1.45 Gm. of tartar emetic the failures were 50 per cent, and as the total dose was increased the failures were decreased until in a group receiving 2.2 Gm. or 444 cc. of ½ per cent solution of tartar emetic the failures were negligible. We now recommend this amount in *S. japonicum* infections, and 500 cc. in patients with central nervous system involvement or failure following the initial course of treatment. Tartar emetic is more toxic than fuadin and more troublesome to administer since the solution should be freshly made and must be given slowly intravenously, whereas fuadin is given intramuscularly. In *S. mansoni* infections we recommend 5.0 cc. doses daily, or as closely spaced as possible until 100 cc. are given. Stool examinations should be started a month after completion of therapy and continued weekly for at least 6 months or more using techniques specially devised for schistosome eggs.

Several years ago, Alves and Blair[24] reported a high percentage of

cures in both *S. mansoni* and *S. haematobium* infections following three intravenous injections daily of 120 mg. of sodium antimony tartrate for 2 days. We have treated several patients with *S. japonicum* infections in this manner without benefit. Similarly we found intensive pentavalent antimony therapy ineffective, although in *S. mansoni* infections good results have been reported from the use of such drugs. The short intensive course of treatment with sodium antimony tartrate is being used in Egypt, but toxicity is considered a serious drawback to its routine use in villages and cure rates are not yet available.

Most recently Miracil D, a thioxanthone derivative administered by mouth, has been under investigation in Egypt in the treatment of both schistosomiasis mansoni and haematobium by Watson, Abdel Azim and Halawani.[25] In animals suitable dosage administered for a sufficient length of time resulted in disappearance of eggs from urine and stools, and at autopsy disintegrating or dead worms were found. In man the best results were obtained with 300 mg. given at 12 hour intervals for from 5 to 14 days in one or more courses. Although the ultimate absolute cure rates observed were very low, the patients showed clinical improvement and apparent reduction in the number of surviving or sexually active worms. No major or serious toxicity is reported in this study. The demonstration of effectiveness, however slight, of a drug by mouth in a disease such as schistosomiasis is a great stimulus in the chemotherapy of an infection so difficult to control, and it is hoped that continued search will reveal a truly curative oral agent.

Closing Remarks

It is evident from my remarks this evening that the treatment of parasitic infections is not the hocus pocus imagined by many. It is also evident that the therapy of parasites has a long historic background of productive research which has furnished us with specific agents so that on the whole treatment of most of the infections is satisfactory. Continued investigation is providing us all the time with better drugs. There are deficiencies and hopes for improvement.

In the field of malaria we need a truly causal prophylactic which also is active in terminating clinical activity with definitive cure. However, even now with 4-amino quinolines, chlorguanide, and 8-amino quinolines it is possible to suppress, treat and cure vivax and falciparum infections.

In the field of amebiasis we need better understanding of the significance of the host parasite relationship in regard to carrier state versus actual disease. We need better understanding of the role of bacteria in the growth requirements of amebae and possible relation to pathogenicity. We need bacteria-free cultures to study the organism. We need better methods of diagnosis and a critical evaluation of currently used drugs, as well as better drugs which are universally active against intestinal and other forms of amebic infections.

As far as the worms are concerned, the situation is hopeful. In some instances we need drugs where no effective ones are available. In other infections we need more effective drugs or agents which are less toxic and more easy to administer.

REFERENCES

1. Shannon, J. A. The study of antimalarials and antimalarial activity in the human malarias, *Harvey Lect.*, 1945-1946, *41*:43.
2. Most, H. and Hayman, J. Relative efficiency of quinacrine (atabrine) and quinine in treatment of acute attacks of vivax malaria, *Am. J. M. Sc.*, 1948, *211*: 320.
3. Most, H., London, I. M., Kane, C. A., Lavietes, P. H., Schroeder, E. F. and Hayman, J. M., Jr. Chloroquine for treatment of acute attacks of vivax malaria, *J.A.M.A.*, 1946, *131*:963.
4. Most, H., Kane, C. A., Lavietes, P. H., London, I. M., Schroeder, E. F. and Hayman, J. M., Jr. Combined quinine-plasmochin treatment of vivax malaria: effect on relapse rate, *Am. J. M. Sc.*, 1946, *212*:550.
5. Alving, A. S., Craige, B., Jr., Jones, R., Jr., Whorton, C. M., Pullman, T. N. and Eichelberger, L. Pentaquine (SN-13, 276), a therapeutic agent effective in reducing the relapse rate in vivax malaria, *J. Clin. Investigation*, 1948, *27*, no. 3, pt. 2: 25.
6. Straus, B. and Gennis, J. Evaluation of pentaquine as a cure of relapsing vivax malaria; a controlled study of ninety-five cases, *Bull. New York Acad. Med.*, 1948, *24*:395.
7. Coggeshall, L. T. and Rice, F. A. Cure of chronic vivax malaria with pentaquine, *J.A.M.A.*, 1949, *139*:437.
8. Shookhoff, Howard B. *Personal communication.*
9. Hauer, A. Experiences with a new drug in amoebiasis, *Trop. Dis. Bull.*, 1943, 40:913.
10. Berberian, D. A. Effectiveness of bismuthoxy-p-N-glycolylarsanilate (Win-1011) in the treatment of intestinal amoebiasis. Read by title, 40th Annual Meeting of the American Society for Clinical Investigation, May 1948.
11. Conan, N. J., Jr. Chloroquine in amoebiasis, *Am. J. Trop. Med.*, 1948, *28*:107.
12. Conan, N. J., Jr. The treatment of hepatic amoebiasis with chloroquine, *Am. J. Med.*, 1949, *6*:309.
13. Murgatroyd, F. and Fairley, N. H. Cited by Dr. Neal J. Conan, Jr.[12]
14. Dwork, K. G. The use of para-aminobenzoic acid in amoebiasis; preliminary report, *Bull. New York Acad. Med.*, 1948, *24*:391.
15. Faust, E. C. *Personal communication to Dr. Frank L. Meleney.*
16. Longacre, A. *Personal communication.*
17. Most, H. *et al. Unpublished data.*
18. Most, H., Hayman, J. M., Jr. and Wilson, T. B. Hookworm infections in troops returning from the Pacific, *Am. J. M. Sc.*, 1946, *212*:347.
19. D'Antoni, J. *Personal communication.*

20. Shrapnel, B. C. Oral emetine in the treatment of intestinal amebiasis, *Am. J. Trop. Med.*, 1947, *27*:527.

21. Santiago-Stevenson, D., Oliver-Gonzalez, J., and Hewitt, R. I. Treatment of filariasis bancrofti with 1-diethylcarbamyl-4-methyl-piperazine hydrochloride ("hetrazan"), *J.A.M.A.*, 1947, *135*:708.

22. Culbertson, J. T. The elimination of the tapeworm Hymenolepis fraterna from mice by the administration of atabrine, *J. Pharmacol. & Exper. Therap.*, 1940, *70*:309.

23. Brown, H. W. Recent developments in the chemotherapy of helminthic diseases, Fourth International Congresses on Tropical Medicine and Malaria, *Proceedings*, 1948, *2*:75.

24. Alves, W. and Blair, D. M. Schistosomiasis; intensive treatment with antimony, *Lancet*, 1946, *1*:9.

25. Watson, J. M., Abdel Azim, M. and Halawani, A. Investigations on the antibilharzial action of miracil D. (nilodin), *Tr. Roy. Soc. Trop. Med. & Hyg.*, 1948, *42*:37.

The New York Academy of Medicine

Its First Hundred Years

BY PHILIP VAN INGEN

New York: Columbia University Press, 1949

A Review

This admirable history of the first century of The New York Academy of Medicine is a story of engrossing interest to the Fellows and Friends of the Academy as well as to members of the medical profession generally. The one hundred years embraced by this narrative provide in effect a comprehensive picture of American medicine during its most significant period.

The story opens with a brief account of the founding of the Academy which followed upon a meeting of "the regular practitioners of this city" on December 12, 1846. The invitation to this meeting was extended by Valentine Mott, Alex. H. Stevens and Isaac Wood—men whose standing was preëminent at that time and whose fame has not greatly diminished with the years. The names and the standing of these men who called this preliminary meeting are in a general sense typical of the leaders of the Academy through the ensuing years. So also are the purposes expressed in this invitation: "The design of this call is to ask coöperation of our medical brethren in an undertaking intended to elevate the character of our profession and to advance its interests and increase its usefulness by furnishing facilities for medical intercourse, promoting harmony among its members, and offering means of mutual improvement therein."

It is true that in the succeeding chapters which deal with the achievements, failures and vicissitudes of the Academy there have been times when its gatherings have not been significantly harmonious but honest differences of opinion have not seriously impeded the steady growth and influence of this notable institution. As a matter of fact, many of these dissensions, at the time acrimonious and bitter as they undoubtedly were, can now be reviewed with charity. The author is

especially adept in describing these historic encounters and this he does accurately and impartially, even at times with a delightful humor.

In the succeeding chapters which relate the events and developments of the Academy under its successive presidents, the author has selected so wisely that the reader is granted a perceptive appraisal of the great actors in New York Medicine as well as of significant advances in medicine during the first hundred years of the Academy. Each chapter deals with the term or terms of one or more Presidents and thus we come upon such stirring names as Valentine Mott, Willard Parker, Austin Flint, Fordyce Barker, Abraham Jacobi, Alfred L. Loomis, Joseph D. Bryant, Edward G. Janeway, Charles L. Dana, Walter Belknap James, George David Stewart, Samuel Waldron Lambert, Bernard Sachs, Eugene H. Pool, James Alexander Miller and William Worthington Herrick, to name only a few of the departed leaders whose lives have influenced the progress of medicine in America.

Characteristic of the narrative qualities of this history is the description of the great battle waged during the third term of office of President Fordyce Barker. In appealing to the Fellowship for support Dr. Barker said in summary: "I think that it will be apparent that the whole intent of the proposed amendments is to make the Academy of Medicine a purely scientific society, independent of all other organizations; to place its standard of ethics on a higher plane than before; and to prevent the possibility of any future troubles by the introduction of matters foreign to its advanced objects."

The opposition included such men as the Austin Flints, Sr. and Jr., John H. Hinton and Samuel Purple. A long and bitter struggle followed. In the end the course of Fordyce Barker was sustained. Characteristically the incident is summarized by the author of this book: "The whole thing was a miserable, unfortunate affair, but it established, for all time, the Academy's position as an organization devoted to scientific matters, aloof from all standards of ethics, except as affecting its own organization. It was perhaps worth while."

As the history progresses it becomes apparent that the Academy, which in its beginning could have been described as an exclusive doctors' club, has through the years both broadened and elevated its mission so that more and more it has become an organization dedicated to medical education, public health and the welfare of mankind.

The book is replete with incidents of interest to the profession and

with vignettes of colorful personalities. In a measure it enlightens not only the medical but also the lay history of New York during the century of the city's greatest development and progress.

The style is effectively simple and sincere. The author has spared no pains to ensure accuracy and fidelity to truth. The book is indexed and freely illustrated.

The reader comes not only to appreciate the care exercised by Dr. Van Ingen in this labor of love but to share in his affection for the Academy.

REPORT OF THE SUBCOMMITTEE ON THE PROPOSED MUNICIPAL BOND ISSUE OF $150,000,000 FOR HOSPITALS

I. THE PROPOSITION

On November 8th the citizens of this State will vote on Proposition Seven, which, if approved, will authorize the City of New York to issue bonds for the construction, reconstruction, and equipment of hospitals to the extent of one hundred and fifty millions, in excess of its ordinary debt limit. The existing constitutional provision makes it impossible for the City to issue bonds above 10 per cent of the average assessed valuation of the five years just prior to the floating of the bonds. The proposed Hospital Bond Issue of $150,000,000 applies to New York City exclusively; yet because it amends the State Constitution it will have to be voted on by the entire electorate of the State.

The proposition before the electorate, then, is whether or not the Constitution should be amended to allow a bond issue above the prescribed constitutional limit. This exception, of course, is to apply but once and for the specific purpose. The request for our support of this proposition has come from the State Charities Aid Association and the New York Tuberculosis and Health Association.

II. THE REASON

Up to recently we had no well formulated policy to guide the development of our municipal hospitals. The City of New York, although it established a Department of Hospitals in 1929, in which all the city institutions for the care of the sick were put under one administrative head, had no clear-cut plan with regard to its own hospitals and their relation to the other hospitals of the community.

The financial condition of the City has for years prevented the building of new hospitals and the renovation of existing ones except during the era of large federal grants, from 1933 to the outbreak of the War. During the War no construction of any kind was possible and in the postwar years only such measures were taken as the restricted financial conditions would allow. We have now under construction hospitals which will cost a total of $42,000,000 but the large needs of the older hospitals for renovations have not been met because of the continual demands on the City treasury for other pressing problems. As a result, many of the hospitals are in a bad state of disrepair; moreover, some of them are not fireproof, and many of them are functionally ill-adapted to the demands of modern medicine. Even hospitals which were built less than 20 years ago are in some respects obsolescent, and the buildings dating back from 50 to 100 years are almost impossible to adapt to the needs of today. Not only are the facilities in these hospitals clumsily arranged for efficient

operation, but, because of that, the cost of operation itself has greatly increased.

At the same time the demands on the hospital are increasingly heavy and in many of them the patient-load is considerably above the operating capacity for which the facilities were designed.

There is no doubt that many of the municipal hospitals require a thorough overhauling and most of them must be modernized to operate effectively and economically.

III. PROPOSED PLANS

Much thought has been given to the projected developments which have been harmonized to a large extent with the basic ideas of the Master Plan of the Hospital Council of Greater New York, not only as to geographical location of the future hospitals but also with regard to functional purposes. Although it is not a matter of immediate importance insofar as the principal question is concerned, it should be pointed out that, because of the proposed abandonment of many of the existing beds, the total bed capacity of the municipal hospitals will not be greatly increased, if at all, after the $150,000,000 have been expended on the projects in mind. When the entire program is completed, including the $42,000,000 construction now under way, the total increase will be about 2,600 beds. What is important, however, is that the hospitals will be safe from the standpoint of hazard, and modern from the standpoint of efficient functioning, both clinically and administratively. The building program will likewise result in a reshifting of facilities for the accommodation of patients. Many of the present general-care hospitals are overcrowded, chiefly because of the great number of patients with long-term conditions; these patients would be dealt with effectively in special units to be provided, or through the home-care program, or through the outpatient departments, or, in some cases, in custodial care accommodations. The proposed reshifting of the patient-load, both geographical and functional, should result in an improvement in the care of the sick in the municipal hospitals. Allied with general care, there will be a considerable increase in accommodations for the care of tuberculous patients, for cancer patients, for psychiatric patients, and for the category generally designated as "chronics."

There are some items in the program which may perhaps be changed or modified, or even abandoned, but this is not the moment to discuss these problems, for, as has been stated, the main issue is "To be or not to be," insofar as the ability of the City to build the hospitals is concerned.

IV. APPROVAL OF THE BOND ISSUE

For the reasons stated herein, this Subcommittee is of the opinion that the Academy of Medicine should place itself squarely in favor of the proposed Bond Issue and make its position known to the public through every means at its disposal. It may be added that the Medical Society of the State of New York as well as the Medical Society of the County of New York has voted to support Proposition No. Seven.

S. BAYNE-JONES, *Chairman;* JAMES R. REULING, DICKINSON W. RICHARDS, IRWIN E. SIRIS, MAXIMIN DEM. TOUART, E. H. L. CORWIN, *Secretary.*

Approved by the Committee on Public Health Relations of The New York Academy of Medicine on October 3, 1949.